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PHYSIOLOGIC EFFECTS OF HIGH CONCENTRATIONS OF OXYGEN IN EXPERIMENTAL SECONDARY SHOCK

HARRY A. DAVIS, M.D.
NEW ORLEANS

Despite the widespread use of oxygen therapy for clinical shock, few studies have been made of the effect of high concentrations of oxygen in experimental shock. The rationale of the method is based on the fall of oxygen consumption associated with hemorrhagic and traumatic shock, which was first pointed out by Aub and Cunningham¹ and which has since been confirmed by many other workers. The present report concerns a series of experiments undertaken to investigate the physiologic action of high concentrations of oxygen on normal control animals and experimental animals in which secondary shock had been produced.

MATERIALS AND METHODS

Dogs weighing from 10 to 25 pounds (4.5 to 11.3 Kg.) were kept under light anesthesia produced by intravenous injection of pentobarbital sodium in doses of $\frac{1}{4}$ grain (0.015 Gm.) per kilogram of body weight. The arterial blood pressure was recorded with a mercury manometer by means of a cannula inserted in the right carotid artery. Studies made on blood withdrawn from the femoral artery and vein consisted of red and white cell counts, determination of the level of hemoglobin (Sahli), hematocrit readings and estimation of the values for sugar, nonprotein nitrogen, sodium chloride, carbon dioxide-combining power and oxygen content. The blood for the gas determinations was withdrawn under oil.

Hemorrhagic shock was produced by bleeding the animal through the cannula inserted into the carotid artery. It was thus possible to study the response to administration of oxygen in shock associated with hemodilution. Shock associated with hemoconcentration was produced by the method described by me,² which consists of injection of

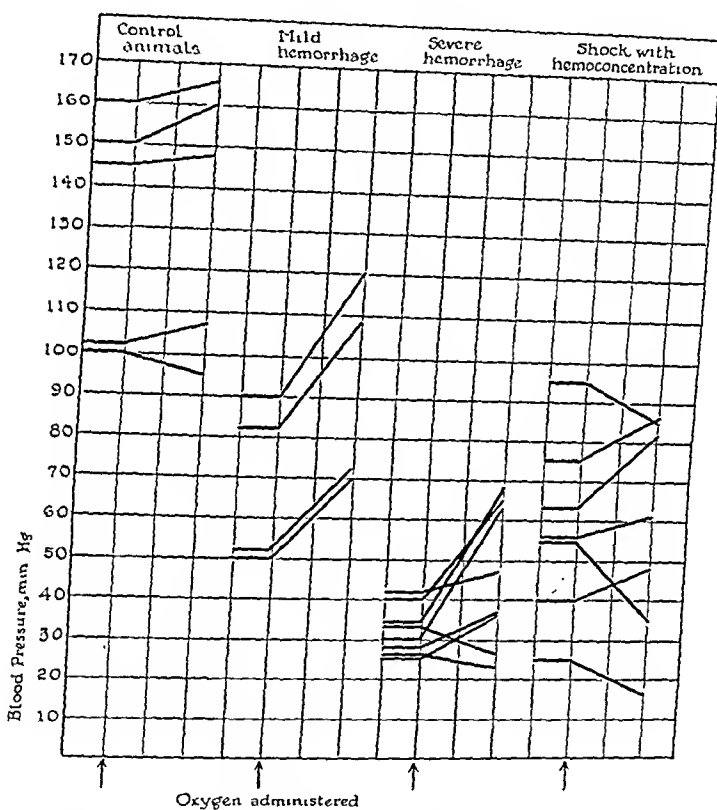
From the Department of Surgery of the School of Medicine of Louisiana State University.

1. Aub, J. C., and Cunningham, T. D.: Studies in Experimental Traumatic Shock: II. The Oxygen Content of the Blood, *Am. J. Physiol.* **54**:408-415, 1920.

2. Davis, H. A.: Acute Circulatory Failure (Shock) Following Subcutaneous Injection of Hypertonic Sodium Chloride Solution, *Proc. Soc. Exper. Biol. & Med.* **43**:354-357, 1940.

25 per cent sodium chloride solution subcutaneously in doses of 25 cc. per kilogram of body weight. The shock produced by this procedure closely resembles that which follows trauma, but the effects are more uniform and more constant. After the injection of hypertonic sodium chloride solution the blood pressure does not fall to the shock level until three or four hours has elapsed.

Oxygen was administered in amounts of 1,000 cc. per minute for fifteen minutes by a tube inserted into the trachea through a tracheotomy opening. It was humidified by passage through water, and the flow was regulated by means of a flow meter.



Influence of administration of oxygen on blood pressure.

PHYSIOLOGIC EFFECTS OF OXYGEN IN NORMAL ANIMALS

Blood Pressure.—In the majority of instances the administration of oxygen to normal animals produced no changes in the blood pressure. Occasionally a slight fall occurred, and a rise of 2 to 5 mm. of mercury was sometimes observed (chart).

Pulse Rate.—A slowing of the pulse rate, which varied from 4 to 20 beats per minute, was frequently observed following the administration of oxygen. The mechanism of the diminution is not clear at this time.

Blood Changes.—Determinations of the hemoglobin content of the blood by the Sahli method showed slight increases, varying from 1 to 3 per cent, following the administration of oxygen. Hematocrit determinations revealed similar slight increases in the amount of the cellular elements. The red blood cells were also slightly increased in number, the increases being in the neighborhood of 200,000 to 300,000 per cubic millimeter. The increases in the amount of hemoglobin and in the number of red blood cells were not great, but their uniform occurrence after the administration of oxygen to normal animals suggests some definite

TABLE 1.—*Influence of Administration of Oxygen on Blood of Control Animals*

Dog	Red Blood Cells (in Millions) per Cu. Mm.		Hemoglobin, per Cent		Hematocrit, per Cent		White Blood Cells, per Cu. Mm.	
	Before Oxygen	After Oxygen	Before Oxygen	After Oxygen	Before Oxygen	After Oxygen	Before Oxygen	After Oxygen
5	5.65	6.3	78.5	81	52	54	6,150	6,100
1	4.68	4.98	55.5	58	29	30	16,000	13,000
2	5.92	5.8	84.5	88	37.5	37	11,500	10,050
3	5.94	6.21	79	90	45	46	7,225	4,800
4	6.23	6.72	100	103	54.9	56	5,750	4,800

TABLE 2.—*Influence of Administration of Oxygen on Blood Gases of Control Animals*

Dog	CO ₂ -Combining Power (Arterial Blood), Volumes %			Oxygen Content (Arterial Blood), Volumes %		
	Before Administration	Immediately After Administration	15 Minutes After Administration	Before Administration	Immediately After Administration	15 Minutes After Administration
4	20.3	20	18.2	19.6	22.8	21.37
3	44	29	25	21.2	25.5	24.4
2	55	54	51	18.5	20	21
5	29.5	26	18	19.71	22.59	19.49
1	54	30	47	19.4	27.15	18.15
18	35.5	32.7	36.8	17.76	19.53	18.58

relation between them. The white blood cells were definitely reduced in number, the reduction varying from 10 to 30 per cent of the initial number. The decrease in the number of leukocytes was thus relatively greater than the increase in the number of red blood cells (table 1).

Little change was observed in the blood sugar, the nonprotein nitrogen of the blood and the blood chlorides (determined as sodium chloride) after the administration of oxygen. The carbon dioxide-combining power of the blood was definitely decreased, and the decrease was maintained for as long as twenty minutes after the administration of oxygen was discontinued (table 2). The data available thus demonstrate the strange fact that the administration of oxygen causes an increase in the amount of carbon dioxide in the blood. Although this phenomenon,

which has been observed by other workers, has been attributed to defects in the respiratory apparatus, certain other possibilities suggest themselves. It may be due to the stimulation of tissue metabolism resulting from the increased oxygen content of the blood. It may be a homeostatic response designed to increase the utilization by the tissues of the increased amount of oxygen in the blood, an explanation which would seem to be supported by the work of Bohr and his associates,³ who showed that the dissociation of oxygen from oxyhemoglobin takes place more rapidly in the presence of increased amounts of carbon dioxide in the blood.

The oxygen content of the blood was increased after the administration of oxygen, the increases varying from 10 to 50 per cent above the initial level. The increase was not maintained, however, as was the alteration in the carbon dioxide-combining power, and within fifteen to twenty minutes after the oxygen had been discontinued the oxygen content of the blood had returned to the original level (table 2).

Before proceeding further it is necessary to consider the effects in these control animals of the administration of oxygen on the coefficient of oxygen utilization (C. O. U.), which is the amount of oxygen utilized by an organ or tissue in any given period. It is obtained by subtracting the venous oxygen content from the arterial oxygen content and dividing the result by the arterial oxygen content, the oxygen content being calculated as volumes per cent. The formula may be represented simply by

$$\frac{A_o - V_o}{A_o} \times 100 = \text{C. O. U. (in volumes of oxygen per cent)}$$

An increase in the coefficient of oxygen utilization indicates an increased utilization of oxygen by the tissues, due either to an increase in their rate of metabolism or to a decrease in the rate of blood flow through the area under consideration, which would allow more oxygen to diffuse from the blood to the tissues. Conversely, a decrease in the coefficient indicates a decreased utilization of oxygen by the tissues, due either to a diminution in the rate of metabolic activity of the tissue or to an increase in the rate of blood flow through the area, which would permit less oxygen to be given off from the blood to the tissues.

The administration of oxygen to control animals produces a decrease in the coefficient of oxygen utilization, which, if one assumes that no alteration occurs in the ability of the tissues to utilize oxygen, must be the result of an increase in the rate of blood flow (table 3).

3. Bohr, C.; Hasselbalch, C. B. K., and Krogh, A.: Ueber den Einfluss der Kohlensäurespannung auf die Sauerstoffaufnahme im Blute, *Zentralbl. f. Physiol.* **17**:661-664, 1903. Hasselbalch, C. B. K., and Krogh, A.: Ueber einen in biologischer Beziehung wichtigen Einfluss, den die Kohlensäurespannung des Blutes auf dessen Sauerstoffbindung übt, *Skandinav. Arch. f. Physiol.* **16**:402-412, 1904.

TABLE 3.—*Influence of Administration of Oxygen on Oxygen Content of Blood and Coefficient of Oxygen Utilization (C. O. U.) in Shock*

	O ₂ Content, Volumes % Arterial	Venous	A-V Differ- ence	C. O. U., Volumes %	O ₂ Content, Volumes % Arterial	Venous	A-V Differ- ence	C. O. U., Volumes %	O ₂ Content, Volumes % Arterial	Venous	A-V Differ- ence	C. O. U., Volumes %
Control.....	17.76	Initial 12.43	5.43	30.5	19.53	After O ₂ 13.65	5.88	30.1	18.58	13.21	5.37	28.7
Control.....	17.56	Initial 13.56	4.4	24.4	20.61	After O ₂ 15.76	4.85	23.5	17.02	13.01	4.01	23.5
Mild hemorrhage.....	19.98	Initial 10.58	9.1	45.5	16.43	After hemorrhage 9.31	7.09	13.1	18.2	11.99	6.21	34.1
Mild hemorrhage.....	23.32	Initial 17.92	5.4	23.1	19.06	After hemorrhage 14.73	4.33	22.7	22.4	17.51	4.89	21.6
Severe hemorrhage.....	16.2	Initial 12.15	4.05	23.0	12.77	After hemorrhage 9.06	3.71	20.05	14.13	11.67	2.46	17.1
Severe hemorrhage.....	18.79	Initial 11.72	7.07	37.6	15.45	After hemorrhage 8.88	6.55	42.1	17.31	9.41	7.8	45.3
Shock with hemoconcentration.....	16.76	Initial 12.32	4.44	26.1	18.09	After shock 11.98	6.11	33.7	19.42	11.3	8.12	17.8
Shock with hemoconcentration.....	11.61	Initial 12.32	2.32	16.8	18.01	After shock 14.96	3.08	17.0	19.53	15.17	4.36	22.3

PHYSIOLOGIC EFFECTS OF OXYGEN IN HEMORRHAGIC SHOCK

Mild Hemorrhagic Shock.—The administration of oxygen to animals in which the blood pressure had been lowered to 50 to 90 mm. of mercury by graded hemorrhage caused a moderate rise of blood pressure, varying from 10 to 30 mm. (chart). The pulse rate, which had been accelerated by the bleeding, became slightly slower after the administration of oxygen. No constant alteration was observed in the blood constituents, but the carbon dioxide-combining power of the blood was diminished and the oxygen content slightly increased.

The carbon dioxide-combining power of the blood, which had diminished after the production of hemorrhage, was still further decreased by the administration of oxygen. A slight increase in the oxygen content of the blood was observed in some animals after the production of hemorrhage, but in most instances the oxygen content of both the arterial and the venous blood diminished slightly. The admin-

TABLE 4.—*Influence of Administration of Oxygen on Blood Gases in Hemorrhagic Shock*

Dog	CO ₂ -Combining Power, Volumes % (Arterial Blood)			Oxygen Content, Volumes % (Arterial Blood)		
	Initial	After Hemorrhage	After Oxygen	Initial	After Hemorrhage	After Oxygen
8	26	16	13.3	18.76	11.51	12.4
11	27.2	19.4	9	18.79	15.43	17.21
16	32	21	14	16.2	10.91	12.5
23	21	13.5	9.5	19.98	16.43	18.2

istration of oxygen resulted in increases in the oxygen content averaging 1.7 volumes per cent.

Hemorrhage sufficient to produce a mild degree of circulatory failure resulted in a diminution of the coefficient of oxygen utilization, which, assuming that the metabolic needs of the tissues did not vary over the experimental period, suggests the occurrence of an increased rate of blood flow. The administration of oxygen resulted in a further diminution of the coefficient (table 3). It seems reasonable to assume, therefore, that oxygen accelerates the rate of blood flow in animals suffering from mild circulatory failure due to hemorrhage.

Severe Hemorrhagic Shock.—Examination of the blood of animals in which the blood pressure had been lowered to 15 to 40 mm. of mercury by bleedings repeated until the pressure showed no tendency to rise above these levels revealed the usual changes associated with severe hemorrhage. The carbon dioxide-combining power was markedly lowered, especially when the shock had persisted for some time, and the oxygen content of both the arterial and the venous blood was greatly diminished (table 4). The coefficient of oxygen utilization was

increased, which, again assuming that the metabolic requirements of the tissues were not altered during the experimental period, suggests the occurrence of a diminished rate of blood flow (table 3). It is clear, therefore, that oxygen utilization differs in mild and in severe hemorrhagic shock.

When oxygen was administered to animals in severe hemorrhagic shock, an increase in blood pressure usually occurred, varying from 5 to 30 mm. of mercury (chart). The effect was more pronounced when the state of shock had not been allowed to exist too long (more than thirty minutes). In some animals a further fall of blood pressure resulted from the administration of oxygen. It was noted that the continuous administration of oxygen to animals with blood pressures varying from 15 to 25 mm. of mercury was capable of prolonging their lives. The maintenance value of continued administration of oxygen in the presence of low levels of blood pressure due to hemorrhage, as will be emphasized later, may have some clinical significance.

The administration of oxygen causes some slowing of the heart rate in cases of severe hemorrhagic shock. When the blood pressure is greatly lowered and the heart rate slow and irregular it may cause an improvement in the pulse rate parallel with the rise in blood pressure.

Both the carbon dioxide-combining power and the oxygen content of the blood were altered by the administration of oxygen, though no constant effects on the blood constituents were noted. The carbon dioxide-combining power, which had fallen after repeated bleedings, was still further reduced by the administration of oxygen. The oxygen content of the blood was moderately increased, the average increase being 1.5 volumes per cent (table 4). The response of the coefficient of oxygen utilization to oxygen varied. When oxygen was administered after the period of lowest blood pressure had existed for less than thirty minutes the coefficient was decreased, which suggests that the rate of blood flow increased through the tissue under consideration. When, however, the period of low blood pressure exceeded thirty minutes, the coefficient was increased by the administration of oxygen, which may indicate a decrease in the rate of blood flow and the consequent escape of more oxygen from the blood to the tissues (table 3). It is evident, therefore, that the degree and duration of the reduction of the blood pressure in cases of severe hemorrhagic shock have an important bearing on the response to administration of oxygen.

The question arises as to the effect on the oxyhemoglobin dissociation curve of the extreme dilution of the blood which occurs in hemorrhage. The increase in the coefficient of oxygen utilization in the presence of severe hemorrhagic shock suggests that the dissociation of oxyhemoglobin is not decreased. Richards and Strauss⁴ observed that

4. Richards, D. W., and Strauss, M. L.: *Oxy-Hemoglobin Dissociation Curves of Whole Blood in Anemia*, J. Clin. Investigation 4:105-126, 1927.

the oxyhemoglobin dissociation curves for whole blood in the presence of severe primary and secondary anemias were similar to those for normal blood when the pH was normal or slightly lowered. Since in cases of severe hemorrhage acidosis is present and the pH of the blood is lowered, the conditions would seem favorable for the normal dissociation of oxyhemoglobin.

PHYSIOLOGIC EFFECTS OF OXYGEN IN SHOCK
ASSOCIATED WITH HEMOCONCENTRATION

In animals in which shock associated with hemoconcentration was produced by the injection of hypertonic salt solution, the blood pressure was maintained at the initial level for three or four hours. During this period the blood exhibited profound changes. Within an hour after the injection an increasing hemoconcentration was observed. The blood sugar and the nonprotein nitrogen rose above normal levels. The

TABLE 5.—*Influence of Administration of Oxygen on Blood Gases in Shock Associated with Hemoconcentration*

Dog	CO ₂ -Combining Power, Volumes % (Arterial Blood)			Oxygen Content, Volumes % (Arterial Blood)		
	Initial	After Shock	After Adminis- tration of Oxygen	Initial	After Shock	After Adminis- tration of Oxygen
7	34.1	17.1	14	18.6	16.09	23.09
19	35.6	14.5	11.4	21.26	10.63	17.27
20	20.9	14	11.6	32.5	21.76	24.2
21	38.0	13.72	7.32	18.7	16.09	19.42
22	36	28.5	15.3	14.61	12.43	16.87

carbon dioxide-combining power showed a marked diminution, and the oxygen content, despite an occasional temporary rise, progressively diminished, reaching very low levels before death (table 5). The coefficient of oxygen utilization was definitely increased, which if it is assumed that the oxygen requirements of the tissues did not alter during the experimental period, can be attributed to a reduction in the rate of blood flow (table 3). Such a reduction would permit the passage of larger amounts of oxygen from the blood to the tissues.

Oxygen was administered after the blood pressure, at the end of the stationary period, had fallen to levels between 55 and 95 mm. of mercury. The results varied. A rise of blood pressure, varying from 10 to 19 mm. of mercury, occurred in some animals. In others the blood pressure remained unaffected, and in still others it was actually lowered, the decreases varying from 5 to 20 mm. of mercury (chart). The effects of oxygen on the pulse rate were so varied that conclusions are not justified.

The constituents of the blood, other than the carbon dioxide-combining power and the oxygen content, were not uniformly affected

by the administration of oxygen. The carbon dioxide-combining power, which was already diminished as the result of the injection of hypertonic salt solution, showed a further decrease when oxygen was administered (table 5). The oxygen content was definitely augmented, the increase in the arterial blood averaging 4.8 volumes per cent, which represents increases ranging to 30 per cent of the initial levels. Examination of the blood fifteen minutes after the administration of oxygen was discontinued revealed that, although the oxygen content had dropped, it was still higher than it had been prior to the administration of oxygen. A definite increase in the coefficient of oxygen utilization occurred, which, if it is assumed that the oxygen needs of the tissues had not altered during the experimental period, suggests that a diminution of the rate of blood flow occurs as the result of the administration of oxygen (table 3).

At this point the question arises as to why the oxygen content of the blood falls in this form of shock, in spite of the increase in the amount of hemoglobin per cubic centimeter of blood. That the decrease is not directly due to some inability of the concentrated blood to absorb oxygen is shown by the greater increase in its oxygen content as compared with the increase in oxygen in normal blood under the same circumstances. It is possible that the diffusion of oxygen through the lungs to the blood may be less efficient when the blood is concentrated. This theory is supported by the work of Ray, Thomas and Strong,⁵ who found in lung perfusion experiments that increasing the number of red blood cells in the perfusion fluid resulted in inadequate oxygenation of the blood. These authors offered four possible explanatory factors: (1) reduction of the rate of diffusion of oxygen through the alveolar capillaries in the presence of hemoconcentration; (2) the longer time taken for complete equilibration of concentrated blood, as determined from dissociation curves; (3) dilatation of the capillaries of the lung in the presence of hemoconcentration, which means that the oxygen must travel an increased distance to complete the process of oxygenation, and (4) distention of the alveolar capillaries, which diminishes the size of the alveoli and, as a result, the amount of air available for oxygen diffusion.

The possibility must also be considered that the threshold of concentrated blood is higher than that of normal blood, so that higher pressures of oxygen than normally exist in air would be required to raise the oxygen content. Finally, the reduction in the rate of blood flow will diminish the oxygen content of the blood, since less blood will pass through the lung for aeration during any given period of time.

5. Ray, G. B.; Thomas, C. I., and Strong, J. E.: The Oxygenation of Concentrated Versus Normal Bloods, *J. Clin. Investigation* **12**:1051-1062, 1933.

COMMENT

An analysis of the results of this investigation reveals that the power of the blood to absorb oxygen in the presence of shock varies according to the type of shock. In the control animals the administration of oxygen resulted in an average increase of 3.5 volumes per cent of oxygen in the arterial blood. In animals with mild hemorrhagic shock the increase was 1.7 volumes per cent, and in animals with severe hemorrhagic shock it was only 1.5 volumes per cent. In animals with shock associated with hemoconcentration, however, the increase was 4.8 volumes per cent. The decrease in the amount of hemoglobin associated with hemorrhage is probably the chief factor in the reduction of oxygen absorption. It has been pointed out that in the presence of mild hemorrhagic shock the coefficient of oxygen utilization is diminished; this is in agreement with the work of Grant,⁶ who showed that therapeutic bleedings of patients suffering from cardiac failure resulted in a diminution of oxygen utilization. The effect of oxygen on the coefficient of oxygen utilization for animals suffering from mild hemorrhagic shock is to reduce still further the level of oxygen utilization, probably as the result of an increase in the rate of blood flow. In this respect my own work substantiates the observations of Wood, Mason and Blalock.⁷

In contrast to the differences in the oxygen content of the blood in the presence of various types of shock, there is a striking similarity between the coefficient of oxygen utilization in cases of severe hemorrhagic shock and in cases of shock associated with hemoconcentration. Such a similarity would seem to indicate that some fundamental process is common to both, in spite of the fact that with one type of shock there is an extreme dilution of the blood, and with the other, an extreme degree of concentration. This common process is probably the marked reduction in the rate of blood flow, an assumption which is further justified by the similarity of the effect of administration of oxygen on the coefficient of oxygen utilization in the two types of shock. The administration of oxygen in these experiments resulted in an increase in the oxygen content of both the arterial and the venous blood and in an augmentation of the utilization of oxygen, but there did not seem to be a definite relation between these effects and the effect of administration of oxygen on the blood pressure. It was frequently observed that the administration of oxygen increased both the amount of oxygen absorbed and the coefficient of oxygen utilization but had

6. Grant, S. B.: Changes in the Blood Oxygen Following Therapeutic Bleeding in Cardiac Patients, *J. Lab. & Clin. Med.* 9:160-165, 1923.

7. Wood, G. O.; Mason, M. F., and Blalock, A.: Studies on the Effects of the Inhalation of a High Concentration of Oxygen in Experimental Shock. *Surgery* 8:247-256, 1940.

no effect on the falling blood pressure, particularly in cases of shock associated with hemoconcentration. The probable explanation of the continued fall of blood pressure in spite of the increase in absorption and utilization of oxygen is that in animals suffering from shock with hemoconcentration the reduction of blood volume by the passage of a plasma-like fluid into the site of injection was continuous until death.

The behavior of the arteriovenous oxygen difference in response to the administration of oxygen varies with the type of shock. In the normal animal the administration of oxygen results in an increase in the arteriovenous oxygen difference (table 3). Hemorrhage, whether mild or severe, causes a reduction, which is usually followed by a further fall if oxygen is administered. An increase in the arteriovenous oxygen difference, however, occurs after the administration of oxygen in instances in which the blood pressure has remained at a low level for a prolonged period and in which there has been an increase in the coefficient of oxygen utilization. An increase in the arteriovenous oxygen difference always occurs in shock accompanied with hemoconcentration and is further increased by the administration of oxygen (table 3).

The effect of oxygen is predominantly vasopressor (chart), in that a rise of blood pressure occurs not only in normal animals but in animals suffering from mild or severe hemorrhage or from shock associated with hemoconcentration. The mechanism of the increase is not completely known, but three possible causes present themselves: (1) an increase in cardiac output; (2) a direct or indirect action on the blood vessels, resulting in vasoconstriction, and (3) an increase in blood volume.

Wood and his co-workers⁷ found an increase in the cardiac output after the administration of oxygen in the animals in which this was searched for. In lower animals the inhalation of oxygen results in a contraction of the cerebral blood vessels (Tinel;⁸ Schmidt⁹). In man also administration of oxygen produces contraction of the cerebral blood vessels (Lennox and Gibbs¹⁰) and of the retinal blood vessels (Cusick and others¹¹). Indirect evidence would therefore suggest that the

8. Tinel, J.: Régulation de la circulation cérébrale à l'inhalation d'oxygène, *Compt. rend. Soc. de biol.* **96**:665, 1927.

9. Schmidt, C. F.: The Intrinsic Regulation of the Circulation in the Hypothalamus of the Cat, *Am. J. Physiol.* **110**:137-152, 1934.

10. Lennox, W. G., and Gibbs, E. L.: The Blood Flow in the Brain and the Leg of Man and the Changes Induced by Alteration of Blood Gases, *J. Clin. Investigation* **11**:1155-1177, 1932.

11. Cusick, P. L.; Benson, O. O., and Boothby, W. M.: Effect of Anoxia and of High Concentrations of Oxygen on the Retinal Vessels: Preliminary Report, *Proc. Staff Meet., Mayo Clin.* **15**:500-502, 1940.

pressor activity of oxygen is due to at least two factors, one of which is an increase in cardiac output and the other of which is vasoconstriction.

It will be noted that a vasodepressor response to oxygen was more often seen in animals suffering from massive hemorrhage or from shock associated with hemoconcentration than in normal animals or animals suffering from mild hemorrhage (chart).

At present no data obtained by direct experiments are available as to the influence of oxygen on blood volume. Indirect evidence based on changes in the erythrocyte count and in the hemoglobin and hematocrit readings (table 1) does not suggest that an increase in blood volume follows the inhalation of oxygen in normal animals.

The close relation which was observed between oxygen utilization and blood pressure in animals with severe hemorrhagic shock can be explained by the fact that in these animals no further diminution of blood volume was taking place; the increase of oxygen utilization was therefore reflected in a rise of blood pressure. In several animals with severe hemorrhagic shock whose blood pressures were stabilized in the neighborhood of 25 to 30 mm. of mercury it was observed that continuous administration of oxygen was able to prevent a further drop of blood pressure for several hours. It would seem that under such conditions oxygen is capable of preventing further falls in blood pressure provided that the reduction of blood volume has ceased, though ordinarily animals with blood pressures maintained at these levels die within an hour.

SUMMARY AND CONCLUSIONS

An investigation has been carried out concerning the effects of the administration of oxygen on normal animals and on animals suffering from hemorrhagic shock and from shock associated with hemoconcentration.

The results suggest that administration of oxygen is most efficacious when the reduction of the blood volume has ceased and is least efficacious in shock associated with a continued decrease in the blood volume.

The best results were obtained in animals with mild hemorrhagic shock. Good results were also obtained in animals with severe hemorrhagic shock, but the administration of oxygen was of relatively little value for animals with shock associated with hemoconcentration, probably because the reduction in the blood volume continued.

The effects of the administration of oxygen on oxygen absorption and oxygen utilization are discussed.

Although the results of this investigation cannot be applied *in toto* to shock in man, certain clinical considerations are implicit in it:

1. It seems clear that the administration of oxygen should be regarded merely as a subsidiary form of treatment in cases of shock.

2. The best results are obtained before a considerable diminution in the blood volume has occurred, regardless of whether shock is associated with hemodilution or with hemoconcentration.

3. The administration of oxygen is useless in cases of severe shock if the blood volume continues to decrease. If the blood volume is low but no further decrease occurs, oxygen may have the effect of stabilizing the low blood pressure and preventing its further fall until other forms of therapy are available.

RESECTION OF THE LIVER FOR HEPATOMA

RICHARD H. WALLACE, M.D.

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Primary cancer of the liver in the absence of cirrhosis is unusual, and most reports on the subject are from autopsy observations. Hepatoma in an otherwise normal liver may originate in the parenchymatous liver cells or in the intrahepatic bile ducts. This tumor may grow slowly for years before it spreads through hepatic vessels or metastasizes widely. The symptoms usually are mild indigestion or disturbance caused by the size and weight of the tumor, but massive intra-abdominal hemorrhage has occurred.

Few surgeons have reported on resectable hepatoma. In the literature I have been able to find 29 cases, in 7 of which the tumor originated in the right lobe. Of the 23 patients who survived operation, there was no later report of 3, and 8 died of recurrence. A primary hepatoma may be encapsulated and appear benign; it may grow very slowly; it may have areas of cystic degeneration, or it may be associated with hemorrhage which goes on to calcification. However, hepatoma originating either in the liver cells or in the bile ducts is at least potentially malignant and should be removed, together with a margin of normal liver tissue. In only 2 cases in which the patients died of recurrence has mention been made of resection through normal tissue, whereas such resection is described in the majority of cases in which the patient remained free of disease. Twelve patients have been reported alive and well after operation—5 for less than two years, 3 for three years and 4 for longer than five years.

Keen¹ in 1892 first reported a successful resection of the liver for solitary adenoma. The tumor was described as measuring $3\frac{1}{2}$ inches (8.8 cm.) vertically and the same transversely, with a breadth of $2\frac{1}{2}$ inches (7.3 cm.) where it joined the liver, at the extreme right border. It contained numerous small cystic areas and was removed by a cautery and finger nail dissection. Four large veins were ligated, and the stump of the liver resembled that of an amputation, having two flaps, which were approximated with deep sutures. The pathologic diagnosis was

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1. Keen, W. W.: On Resection of the Liver with a Report of a Successful Case of Resection of Adenoma of the Bile Ducts, Boston M. & S. J. 126:405-409, 1892.

adenoma of the bile ducts. Later, Keen² reported the patient well without recurrence eight years after resection, and, in addition, he reported a case of resection of an adenoma of the left lobe.

Yeomans³ in 1915 reviewed the literature on resected primary cancer of the liver and reported 16 operative cases, in 6 of which the patient was alive and well from three to seven years after removal of the tumor.

Wright⁴ in 1923 reported from England the removal of a hepatoma the size of a Jaffa orange from the right lobe of the liver of a man of 60. The tumor was excised through normal liver with a knife, and the raw area was packed with gauze. The patient was alive without recurrence thirty-one months later. Wright wrote: "I think the simple method of cutting boldly through liver tissue is quite safe."

Turner⁵ in 1921 resected a portion of the right lobe of the liver, together with the gallbladder, of a boy of 13 who had a liver cell hepatoma. He first placed deep sutures in normal liver tissue and then with a sharp knife excised the tumor with a V excision. Several large vessels were clamped and tied, and the raw edges were approximated. The pathologic diagnosis was liver cell tumor of hepatic origin, with the cells secreting bile and no bile ducts in the substance of the tumor. The specimen is preserved in the Museum of the University of Durham College of Medicine in England. The boy was well one year and ten months after operation.

Schrager⁶ in 1937 presented a paper discussing the pathologic picture and differential diagnosis of adenoma of the liver and reported successful excision of a grapefruit-sized adenoma on a small pedicle in close relation to the suspensory ligament.

Charache⁷ in 1939 published a comprehensive review of the subject of primary carcinoma of the liver, summarizing 14 cases in which operation on the liver had been performed since the last report of Yeomans. To the cases previously cited he added 7 of resection for hepatoma with operative survival.

2. Keen, W. W.: Report of a Case of Resection of the Liver for the Removal of Neoplasm, *Ann. Surg.* **30**:267-283, 1899.

3. Yeomans, F. C.: Primary Carcinoma of the Liver, *J. A. M. A.* **64**:1301-1306 (April 17) 1915.

• 4. Wright, G.: Case Report, *Proc. Roy. Soc. Med. (Sect. Surg.)* **16**:56-58, 1923.

5. Turner, G. G.: A Case in Which an Adenoma Weighing Two Pounds, Three Ounces Was Successfully Removed from the Liver, *Proc. Roy. Soc. Med. (Sect. Surg.)* **16**:43-56, 1923.

6. Schrager, V. L.: Surgical Aspects of Adenoma of the Liver, *Ann. Surg.* **105**:33-43, 1937.

7. Charache, H.: Primary Carcinoma of the Liver, *Am. J. Surg.* **43**:96-105, 1939.

Tinker and Tinker⁸ in 1939 presented an excellent review of the subject of hepatic resection in general and reported the results of experimental study. They pointed out factors favorable to safe resection of the liver:

1. The lobes and subdivisions of the liver are supplied by independent arteries; so one section can be removed without injury to the remaining sections.

2. Anastomoses between blood vessels of different lobes of the liver are free, insuring adequate circulation if a section is cut off from its normal blood supply.

3. Regeneration after removal of liver substance is rapid and quite complete.

Mann⁹ recently reported the results of animal experiments, emphasizing the importance of the portal circulation for restoration of the liver after partial removal.

In the following case the patient was alive and well more than five years after hepatectomy for a grapefruit-sized hepatic cell hepatoma of the right lobe.

REPORT OF A CASE

A 23 year old housewife was admitted to the Pondville Hospital on June 14, 1935.

Chief Complaint.—A lump in the right side had been present for four years.

Present Illness.—Four years before her admission to the hospital the patient first noticed a dragging sensation in her right side and soon discovered a lump. She consulted a physician, who told her that she had a floating kidney and recommended no treatment. Shortly thereafter she had a single episode of pain in the right upper quadrant of the abdomen and stated that she was yellow for a few days. She had had no similar pain since but had avoided fatty foods because they gave her indigestion. The tumor had gradually increased in size; the dragging sensation had become more bothersome; she had become easily fatigued, and she had been unable to carry on her ordinary housework. Several physicians were consulted; and she had been told at various times that she had a floating kidney, a cyst, a renal tumor and an ovarian cyst.

Past History.—The patient was born in Italy, where as a child she had frequent contacts with dogs. She had had malaria twice.

Marital History.—The patient was married at the age of 15 and had three normal children.

Physical Examination.—The patient was pale; a grapefruit-sized tumor was visible opposite the umbilicus, on the right side. When she stood it descended to the right lower abdominal quadrant. The tumor was smooth, rather firm, non-tender and freely movable but could not be moved into the pelvis. It was easily palpated with one hand in the costovertebral angle.

8. Tinker, M. B., and Tinker, M. B., Jr.: Resection of the Liver: Conditions Favorable for Operation; Methods; Experimental Studies, J. A. M. A. **112**:2006-2008 (May 20) 1939.

9. Mann, F. C.: The Portal Circulation and Restoration of the Liver After Partial Removal, Surgery **8**:225-238, 1940.

The heart and lungs were normal. The blood pressure was 126 systolic and 84 diastolic. Pelvic and rectal examination gave negative results.

Laboratory Data.—The red blood cell count was 3,010,000 and the white blood cell count was 8,400 per cubic millimeter. The value for hemoglobin was 60 per cent. The differential count was normal.

The Hinton reaction was negative. The value for nonprotein nitrogen was 30 mg. per hundred cubic centimeters. Renal function was normal. The urine was normal.

Röntgen Data.—The Graham test revealed that the gallbladder was not visible after administration of the dye.

A pyelogram showed the renal shadows normal in position and outline. After the injection of an opaque medium the renal pelves and calices were well demonstrated and were normal.

Examination of the colon by means of a barium sulfate enema showed that the colon filled readily as far back as the cecum. There was definite displacement

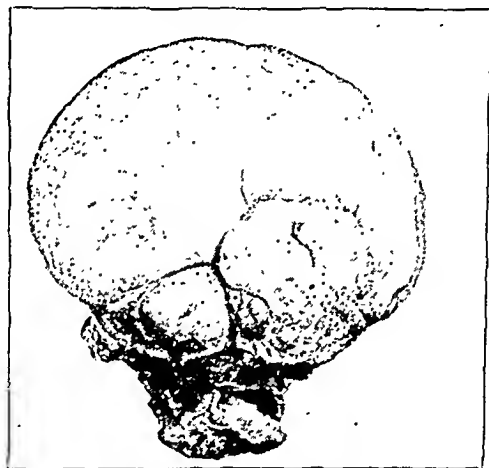


Fig. 1.—Presenting surface of the tumor, which measured 15 by 13 by 5 cm.

of the ascending colon by a tumor mass situated lateral and anterior to it. The mass seemed closely related to the colon, as it moved with the colon when the patient was put in the upright position. There was also slight displacement of the terminal loop of ileum to the midline and downward by the mass, which appeared to have a smooth, rounded contour. The pattern of the mucous membrane was entirely normal in the vicinity of the tumor. This definitely ruled out the possibility of intrinsic tumor of the colon in this case. Films were taken of the tumor mass. In both the anteroposterior and the lateral view a soft tissue tumor about 10 cm. in outline could be identified. In its upper portion a ring of calcium about 4 cm. in diameter was seen. It was situated in the anterior portion of the abdomen, on the right side.

Operation (R. H. W., June 21).—Ether anesthesia was used.

The abdomen was opened through a right paramedian incision. The tumor was dark and firm, with large dilated vessels over it. It involved the right lobe of the liver, and its weight had stretched out the remaining normal liver tissue to a breadth and thickness of 8 cm. There was no liver tissue under the left side

of the diaphragm, as the tumor had rotated the whole liver so that the left margin of the left lobe rested to the right of the midline. An elongated gallbladder containing stones extended over the under surface of the tumor. The other contents of the abdomen were normal. The cystic duct and artery were clamped, cut and tied separately, and the gallbladder was not dissected from the tumor. After an overlapping series of mattress sutures had been placed through normal liver tissue the tumor, with the gallbladder attached, was removed by a wedge-shaped incision with a sharp knife through normal liver tissue. The mattress sutures were

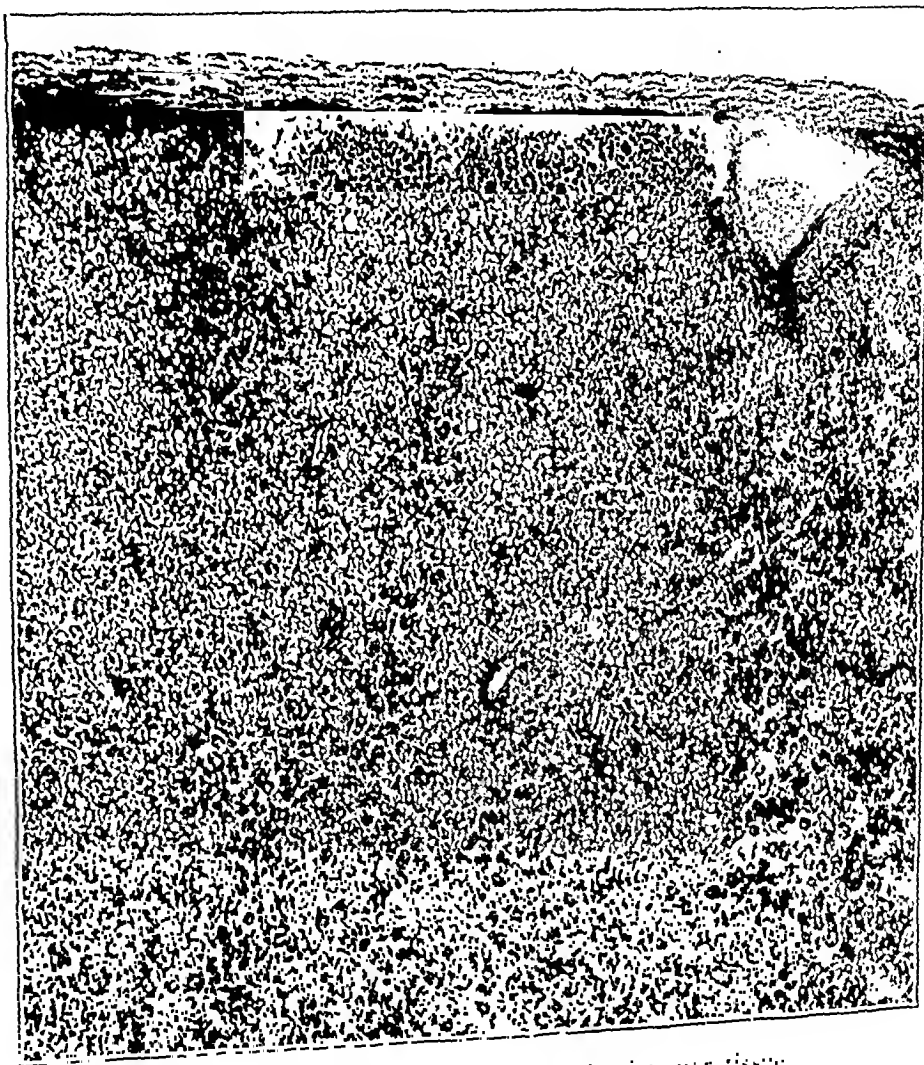


Fig. 2.—Low power photomicrograph of tumor tissue.

tied, and the raw edges were sutured with a running stitch, leaving a dry field. The abdomen was closed with one cigaret wick to Morrison's pouch.

Progress.—There was a small amount of bile-stained serum for three days. The patient had a "flat chart" after seventy-two hours and an uncomplicated convalescence.

Pathologic Report (Dr. Shields Warren).—The specimen was a mass of deep yellowish brown, moderately firm tissue measuring 15 by 13 by 5 cm., It was

covered by thin, smooth serosa traced by large and prominent vessels. The surface was irregularly bossed, with a more elevated, pedunculated portion which was likewise covered by serosa except over one mass measuring 6 by 4.5 by 1 cm. Close to this was the gallbladder, its serosal surface continuous with that over the tumor. It contained a large stone of the mixed type measuring 3 by 1.5 by 0.5 cm. and one smaller stone. The bile was viscid and yellow. The mucosa was reddened. On section, the tumor presented a yellow-brown appearance; here and there it was irregularly streaked with deep red. Close to the broad base of

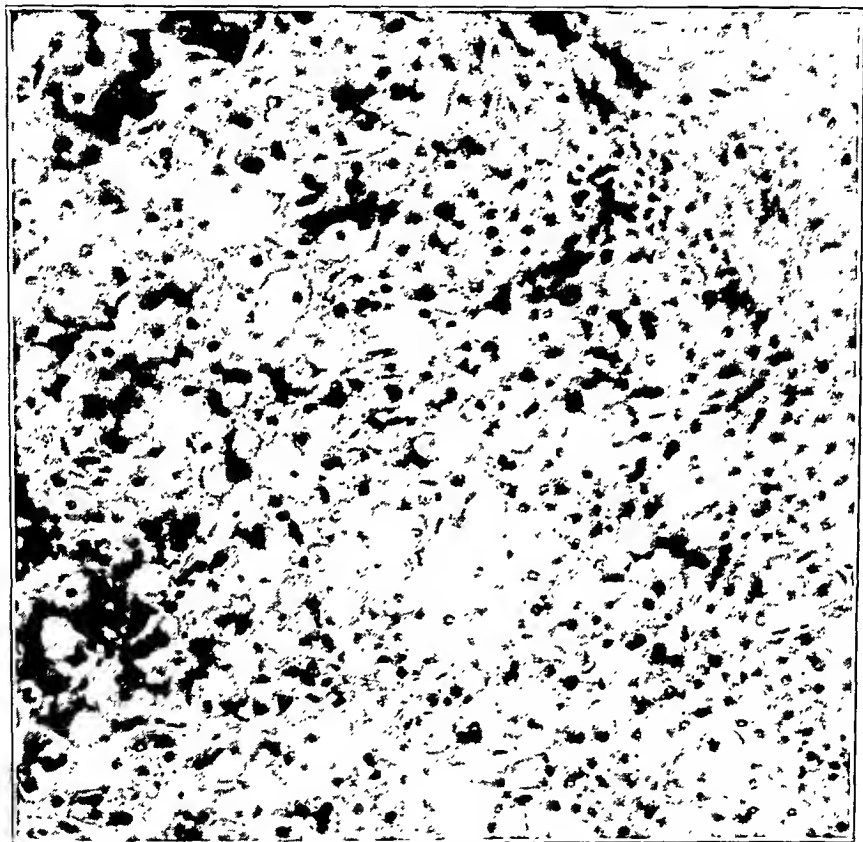


Fig. 3.—High power photomicrograph of tumor tissue.

the fibrous hilus was a focus 3.5 cm. in diameter of reddish, firm clot within a wall 1 mm. thick, white and dense, with calcified foci. A similar but smaller focus (1.7 cm. in diameter) was also present. The tumor substance was soft and friable.

Microscopic Description: The tissue was composed of cords of cells recognizable as hepatic cells, arranged in lobular formation about central veins. The cells were slightly smaller than normal liver cells, and their nuclei were more compact. The portal spaces contained an artery and a vein, but no bile ducts could be made out.

The diagnosis was hepatoma.

Follow-Up.—The patient has reported regularly to the clinic and was last seen by me on July 12, 1940, more than five years after partial hepatectomy. She stated that she had been perfectly well, with no more weakness, discomfort or indigestion. Since two months after her operation she had been able to care for her home and family, which she had previously been unable to do. Examination revealed her to be healthy appearing, with a solid scar and no sign of recurrence.

SUMMARY AND CONCLUSIONS

A patient with a large solitary liver cell hepatoma is reported alive and well more than five years after partial resection of the liver.

Solitary hepatoma, even though it may appear encapsulated and benign, is malignant and should be removed, together with a margin of normal liver tissue.

264 Beacon Street.

SKIN TRANSPLANTATION BY INJECTION

ITS EFFECT ON HEALING OF GRANULATING WOUNDS

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The injection of minute particles of dermal tissue suspended in saline solution beneath the surface of a granulating wound to stimulate healing of an indolent raw surface is at present an unusual mode of skin transplantation. The method is not new,¹ but it is scarcely known and seldom used. During the past fifteen years I have observed beneficial results from its use in numerous orthopedic cases when attempts at skin grafting by the usual methods either had failed or were deemed inadvisable.

The value of skin transplantation as a therapeutic measure for the replacement of lost surface tissue cannot be discussed at length in such a communication as this; neither do the details in the technic of application or the advantages and disadvantages of the several methods now in common use require extended exposition. Before entering into a detailed discussion of the method proposed in this paper, however, it would seem fitting at least to mention the important contributions which have chronicled the attempts to standardize the technic of various methods.

HISTORICAL REVIEW

Tissue transplantation has been shown by the literature of antiquity to have been practiced on a highly developed scale by the ancients. The Egyptians as far back as 3500 B. C. practiced the grafting of tissue, as is shown by the Ebert papyrus (1500 B. C.); the Sacred Vedas, or holy books, of equal antiquity, reveal that flap and grafting operations were well known to the ancient Hindus. The Kornas, a caste of Hindu potters, made use of grafts from the gluteal region. The skin of the buttocks of the donor was beaten with a wooden shoe until it was red before the graft was taken.²

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1. Pels-Leusden: Ueber abnorme Epithelisierung und traumatische Epithelcysten, *Deutsche med. Wchnschr.* **31**:1340, 1905.

2. (a) Fomon, S.: *The Surgery of Injury and Plastic Repair*, Baltimore, William Wood & Company, 1939. (b) Jones, L. P.: *The History and Technique of Skin Grafting*, *West Virginia M. J.* **6**:5, 1911.

The art spread³ from Egypt and India to the southern parts of Asia, to Persia and Arabia and thence to Greece; afterward, according to Carpue,^{3b} it passed to Calabria and from there to other parts of Italy. Celsus (53 B. C. to 7 A. D.) wrote with authority in his "De medicina" on the transplantation of tissues from one part of the body to another. Galen (130 to 210 A. D.) gave minute instructions regarding the repair of defects about the ears, nose and mouth. He advised the removal of all scar tissue and the approximation of wound margins by sutures and by sticking plaster.⁴

During the Dark Ages what was known of tissue transplantation was forgotten, and it was not until the nineteenth century that the art of free tissue transplantation was resurrected.

In 1869, Reverdin,⁵ a Swiss surgeon, working in Guyon's service in the Hospital Necker, Paris, France, demonstrated the possibility of successfully transplanting pieces of epidermis to a granulating area, and on this demonstration are based the theory and practice of skin grafting as it is done today. His clinical application was prompted by his observation of islands of epithelium in the midst of granulations. As he had accepted Billroth's explanation that these islands arose from proliferation either of the epithelium of the cutaneous glands or of scattered bits of the germinal layer of epidermis, it occurred to Reverdin that epithelization of granulating surfaces might be expedited by the artificial implantation of small islands of epithelium. Accordingly, he took the opportunity to demonstrate the practicability of the procedure for a patient who had lost the skin of his thumb. With the point of a lancet he cut from the patient's arm two morsels of epidermis, each about 1 mm. square, transplanted them onto the granulating surface and immobilized them by means of a strip of lead plaster. Within a few days these transplants proliferated to the margins of the wound. The procedure he termed "*greffe épidermique*."

On Dec. 8, 1869, Reverdin⁵ made his momentous report before the Société Impériale de Chirurgie, in which report he described the procedure in detail. All of his colleagues except Guyon, his teacher, and Marc See regarded the procedure with such skepticism that the significance of the discovery and its surgical possibilities went unrecognized

3. (a) Davis, J. S.: Plastic Surgery, Philadelphia, P. Blakiston's Son & Co., 1919. (b) Carpue, J. C.: An Account of Two Successful Operations for Restoring a Lost Nose, London, Longman, Hurst, Rees, Orme & Brown, 1816. (c) Cotton, F. J., and Ehrenfried, A.: Reverdin and Other Methods of Skin Grafting, Boston M. & S. J. **161**:911, 1909.

4. Fomon.^{2a} Cotton and Ehrenfried.^{3c}

5. Reverdin, J. L.: Greffe épidermique, Bull. Soc. de chir. de Paris **10**:493, 1869.

for the time being. Pollock,⁶ of London, England, however, learning of Reverdin's discovery, put it into practice in May 1870, and so spectacular were the results that they immediately aroused the enthusiasm of the medical fraternity of London.

Successful results were soon reported in Ireland, Scotland,⁷ America,⁸ Germany,⁹ Russia¹⁰ and Italy.¹¹ In 1872 Reverdin¹² again reported, this time on his experience in 50 personal cases and on the results obtained by other surgeons with this type of graft.

As experience grew, much information regarding these grafts was accumulated by various surgeons, and objection was made, as was pointed out by Thiersch¹³ in 1872, on the grounds that healing was slow; that the new tissue was little more than a cicatrix; that the grafts were subject to contraction, and that the result was unsightly. In an endeavor to overcome these disadvantages, Thiersch popularized a method which has since been referred to by his name but of which Ollier¹⁴ gave the first published account in 1872.

Instead of using small grafts (2, 3 and 4 mm. in diameter) as Reverdin did, Ollier used grafts 4, 6 and 8 cm. square or even larger, with which he practically covered the denuded area. These grafts proved to be a distinct advance over Reverdin's small grafts, as the method was simple, the grafts were easily and rapidly applied and large areas could be covered in one operation. Time proved, however, that this method had many of the drawbacks of Reverdin's method. The epithelial cover

6. Pollock, G. D.: Cases of Skin-Grafting and Skin Transplantation, Tr. Clin. Soc. London 4:37, 1871.

7. Gillespie: Case of Skin Grafting, Brit. M. J. 2:603, 1870.

8. Chisolm, J. J.: Skin Grafting, Richmond & Louisville M. J. 10:353, 1870.

9. Czerny, V.: Ueber die Entstehung der Tuberkulose nach Hauttransplantation, Centralbl. f. Chir. 13:18, 1886.

10. Jacenko, A.: Ueber die Transplantation abgetrennter Hautstücke, Med. Jahrb. 3:416, 1871. Lindenbaum: Ueber die Transplantation Vollständig vom Körper getrennter Hautstücke auf granulirende Flächen, Berl. klin. Wehnschr. 8:128, 1871.

11. Albanese, E.: Sul trapiantamento dell' epiderme, Gazz. clin. d. sped. civ. di Palermo 3:206, 1871. Amabile, L.: L'innesto epidermico e la trapiantazione cutanea nella cura della piaghe, Movimento 3:129, 1871. Marcani, cited by Cotton and Ehrenfried.^{3c} Perassi: Rapporto sopra una memoria del Professore Luigi Porta. Sull'innesto epidermico della piaghe, Gior. d. r. Accad. di med. di Torino 37:538, 1874.

12. Reverdin, J. L.: Sur la greffe épidermique, Arch. gén. de méd. 19:277, 555 and 703, 1872.

13. Thiersch: Ueber die feineren anatomischen Veränderungen bei Aufheilung von Haut auf Granulationen, Verhandl. d. deutsch. Gesellsch. f. Chir. 3:69, 1874.

14. Ollier, L.: Greffes cutanées ou autoplastiques. Bull. Acad. de méd. 1:243, 1872; abstracted, Lyon méd. 9:464, 1872.

did not prevent contraction; it was not adaptable to wear, slight pressure causing it to ulcerate or slough, and the transplanted skin was prone to undergo discoloration.

The general dissatisfaction led to the revival of the Indian method of full thickness grafting. Wolfe,¹⁵ of Glasgow, Scotland, in 1875 used it successfully in the reconstruction of a lower eyelid. Krause¹⁶ in 1893 described an improved technic which is practically the same as that employed today, and the method is known as the Wolfe-Krause graft.

Some of the drawbacks of the small thin grafts led Davis¹⁷ in 1914 to introduce his small deep grafts; to overcome some of the drawbacks found by experience to accompany the large deep grafts, Blair¹⁸ in 1928 introduced his thick razor, or intermediate split skin, graft. Because of the advantages these two methods have been shown to possess, they have largely replaced the small thin grafts of Reverdin and the large thin razor grafts of Ollier and Thiersch in free skin transplantation.

OTHER METHODS

Many other methods of employing epithelium for grafting have been suggested. Lusk¹⁹ employed the dried cuticle obtained from blisters induced by a vesicating agent, applying it to the denuded area.

Early in the nineteenth century, Dieffenbach²⁰ reported the successful implantation of hair follicles, but the procedure was later attempted by Wentscher²¹ (1898) without success. Scrapings of surface epithelium²² and shavings of warts, corns and calluses have also been used.²³

Pollock⁶ in 1870 described a method by which he implanted small razor grafts (2 to 4 mm. square) directly into the granulations in much the same way as seeds are planted in the ground. This method was

15. Wolfe, J. R.: A New Method of Performing Plastic Operations, Brit. M. J. 2:360, 1875.

16. Krause, F.: Ueber die Transplantation grosser ungestielter Hautlappen, Verhandl. d. deutsch. Gesellsch. f. Chir. 22:46, 1893.

17. Davis, J. S.: The Use of Small Deep Skin Grafts, J. A. M. A. 63:985 (Sept. 19) 1914.

18. Blair, V. P., and Brown, J. B.: The Use and Uses of Large Split-Skin Grafts of Intermediate Thickness, Surg., Gynec. & Obst. 49:82, 1929.

19. Lusk, Z. J.: Some Additional Facts Relating to Skin Grafting, J. A. M. A. 29:782 (Oct. 16) 1897.

20. Dieffenbach, J. F., cited by Cotton and Ehrenfried.^{3c}

21. Wentscher, J.: Wie lange und unter welchen Umständen bleibt die Lebensfähigkeit der menschlichen epidermiszellen ausserhalb des Organismus erhalten? Centralbl. f. Chir. 25:7, 1898.

22. Sée, M.: Greffe épidermique, Gaz. méd., Paris 25:343, 1870.

23. Hodgen, J. T.: Cell or Skin Grafting, St. Louis M. & S. J. 8:289, 1871.
Leale, C. A.: The Use of Common Warts of the Hand in Skin Grafting, M. Rec. 14:188, 1878.

revised by Braun ²⁴ in 1920. (Unlike the small deep graft of Davis, this implant does not preserve its identity but fuses imperceptibly with the rest of the skin.)

Westhues ²⁵ described a combined superficial and buried method of skin grafting in which he used long thin strips of skin threaded through a needle, weaving them in and out over the granulating area so that part of the graft remained above and part beneath the surface of the wound.

Von Mangoldt ²⁶ in 1895 revived the method of applying pulpified epithelium to the surface of granulating wounds.

From a practical standpoint none of these procedures has been found sufficiently satisfactory to warrant continued use.

In Pels-Leusden's clinic ¹ in Griefswald, Germany, pulpified epidermis was forced into the granulation tissue by means of a small syringe to hasten healing. Reschke ²⁷ made use of this method in treating rodent ulcers. It is this same method which I have found useful in selected cases, and it is one which merits more than random consideration. The result following treatment of an extensive burn of the back and arms of the child in the case reported here cannot be regarded by even the most skeptical as merely accidental.

THE TECHNIC

The area from which the skin for injection is obtained should, if possible, contain skin similar in texture to the skin it is intended to replace. The donor area is prepared the day before the operation by first shaving and then scrubbing thoroughly with soft soap U. S. P. and water, rinsing with sterile water, washing with 70 per cent alcohol and covering with a light aseptic dressing.

Immediately before the operation the area is again thoroughly cleansed with soap and water and then with alcohol followed by ether. The selection of the type of anesthesia will depend principally on the experience of the operator, although I do not believe local infiltration of the donor area to be advisable.

The area from which the skin for transplantation is to be taken is scraped lightly with a sharp knife or a razor, and these scrapings are discarded. The area is then sparingly moistened with physiologic solution of sodium chloride, and small thin sections paralleling the surface

24. Braun, W., cited by Wangenstein, O. H.: *The Implantation Method of Skin Grafting*, Surg., Gynec. & Obst. **50**:634, 1930.

25. Westhues: *Modification der Thiersch'schen Transplantation*, *Centralbl. f. Chir.* **25**:7, 1898.

26. von Mangoldt, F.: *Die Ueberhautung von Wundflächen und Wundhölen durch Epithelaussaat; eine neue Methode der Transplantation*, *Deutsche med. Wchnschr.* **21**:798, 1895.

27. Reschke: *Epithelisierungsversuche*, *Arch. f. klin. Chir.* **121**:233, 1922.

are removed and placed in an unglazed earthenware mortar. These small sections are further divided by cross cutting with a knife and finally by grinding with a pestle, a small amount of physiologic solution of sodium chloride being added before the grinding is begun.

The area is again scraped, more vigorously than before, and the scrapings are placed in a separate container. As the dermal area is entered, oozing of serum and some bleeding occur, intermingling with the minutely divided skin. Cells, serum and blood are scooped up at intervals and placed in a container until a sufficient quantity is obtained for the immediate need. The tissues collected in the separate containers are then combined, and enough saline solution is added to disperse the



Fig. 1.—Method of injecting the finely divided particles of skin beneath the surface of the granulation tissue.

mixture so that it may be readily drawn into a glass syringe. (To lessen the tendency for the syringe to stick during the injection, the piston and the inside of the syringe barrel may be coated with liquid petrolatum.)

A needle with a bore large enough to allow the mixture to pass readily through is fitted to the syringe, and the contents are injected into the granulation tissue immediately beneath the surface (fig. 1). The needle may be carried for some distance from its point of entrance close beneath the surface, slowly infiltrating the tissue with the dermal suspension as the needle advances or as it is withdrawn. The injections should begin at or close to the margin of the wound and should be repeated at regularly spaced intervals until the entire circumference has

been infiltrated, continuing somewhat nearer the center of the wound with each successive cycle.

Each time the needle is withdrawn some bleeding occurs at the puncture site, but this has never been bothersome, and the blood has been left to coagulate on the surface.

REPORT OF A CASE

D. G., a 9 year old Negroess, sustained an extensive burn of her back and arms when, on Nov. 19, 1939, her clothing accidentally caught fire. During the first month treatment with the medicaments commonly used for burns resulted in satisfactory progress, but for the ensuing two and one-half months no further healing was noted.

After this time, three and one-half months after her admission to the hospital, she was seen in consultation because of an increasing contracture deformity of her right arm. Clean, healthy-appearing granulation tissue, somewhat excessive over the lower portion of the back, covered the unhealed area (fig. 2A).

Since prevention of greater contracture and lessening of further deformity of the arm were dependent on a more favorable rate of healing of the cutaneous defect than had taken place in the previous months, it was thought advisable that some method of inducing more rapid healing be adopted. Transplantation of skin by the usual methods and by the method described here were each discussed; the injection method was adopted even though the effects on healing in such a large wound seemed most uncertain.

First Transplantation.—On March 8, 1940, one hundred and ten days after the child's admission to the hospital, the first skin transplantation was made. Ethylene anesthesia was used. Dermal tissue was obtained from an area on the back of the right thigh. Into a band measuring from 3 to 4 cm. at the periphery of the wound on her back and arm the finely divided skin suspended in physiologic solution of sodium chloride was injected (fig. 1). The entire area was then covered with coarse mesh paraffin gauze fixed in place with adhesive tape and a sterile dry dressing. The outer dressings were changed every three to five days as needed, but the coarse mesh paraffin gauze was not disturbed.

During the first ten days there was a decided improvement in the rate of healing. Figure 2B shows the extent of healing on the fifteenth day after the skin transplantation. Since little improvement was noted after the tenth day, it was decided to repeat the transplantation. Therefore, on March 26, on the patient's one hundred and twenty-eighth day in the hospital and eighteen days after the first injection, a second transplantation was made.

Second Transplantation.—The operation was identical with the first; this time the skin used for the injection was taken from the back of the left thigh.

Following this second injection there was a noticeable improvement for the first ten to fifteen days, after which time the rate of further healing noted each time the dressing was changed seemed to be diminishing. Repetition of the injection was at this time purposely postponed until no further improvement could be observed. About the end of the fourth week the healing process seemed to have stopped, and during the succeeding ten days no perceptible improvement occurred. Figure 2C shows the condition of the wound on May 3, thirty-eight days after the second injection and one hundred and sixty-six days after admission.

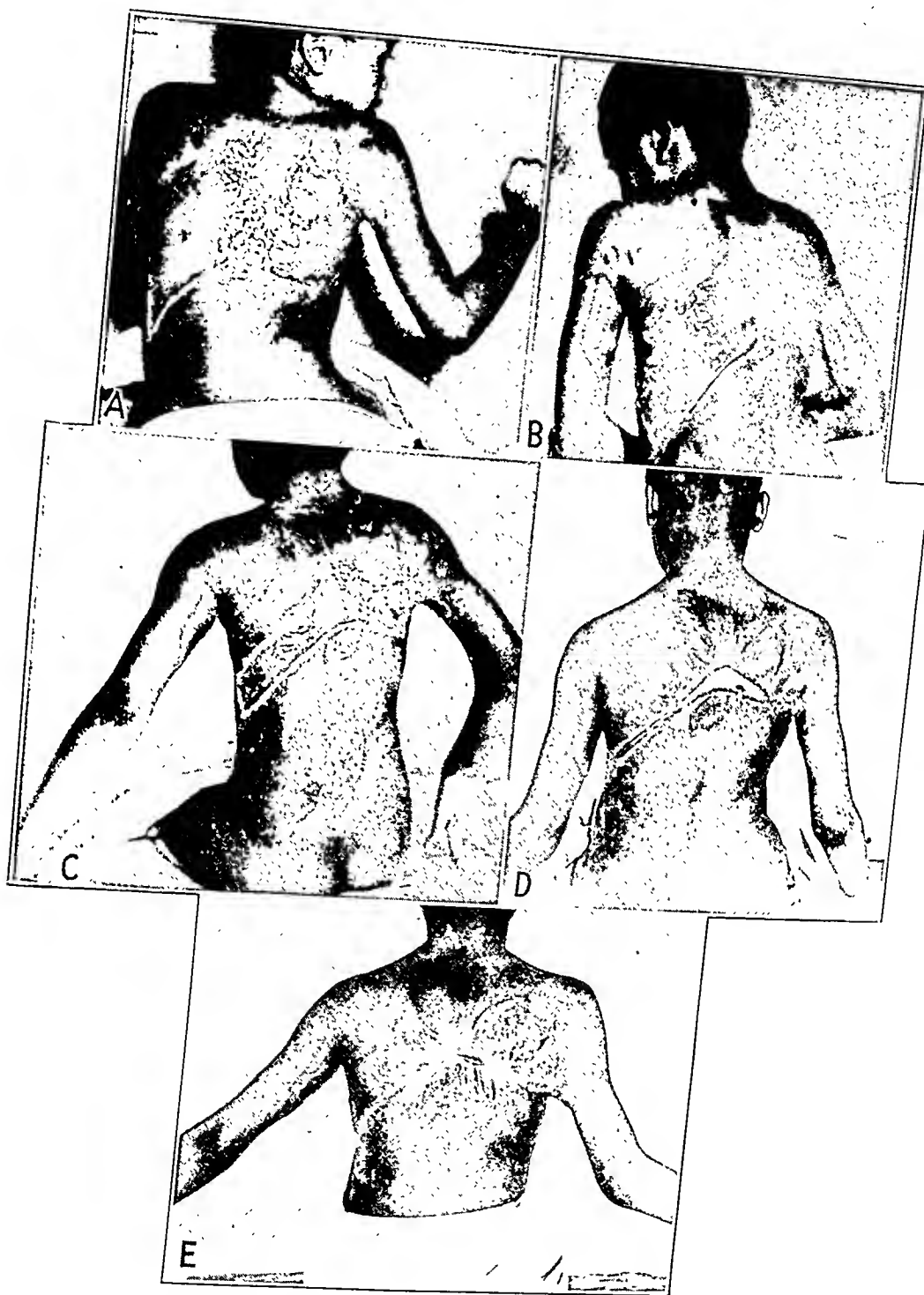


Fig. 2.—*A*, amount of healing which had taken place during the first one hundred and ten days following the accident. This photograph was taken the day before the first skin transplantation. *B*, amount of healing which occurred during the fifteen days following the first skin transplantation. *C*, extent of healing thirty-eight days after the second skin transplantation. *D*, condition of the wound fourteen days after the third dermal transplant, on the day before the child left the hospital. *E*, wound completely healed October 22, one hundred and fifty days after observation of the condition shown in figure 2 *D*.

Third Transplantation.—On the following day (May 4) another injection was made into the periphery of the wound; the skin used was obtained from the back of the left thigh. Three weeks after this third injection healing had become so nearly complete (fig. 2*D*) that continued hospitalization seemed unnecessary; the patient was therefore discharged to the outpatient department for subsequent dressings.

The new skin, as it grew in from the margins of the wound, was lacking in pigment for a short period. The width of this unpigmented band of newly formed skin at the periphery varied with the rate of healing, being widest when and where healing was most rapid and narrowing as healing slowed. Pigmentation in the newly formed skin was eventually uniform and noticeably more abundant than in the undamaged skin elsewhere on the child's body, the healed areas being left darker than the surrounding skin. This was particularly true of the patches on the backs of the thighs where skin had been removed for transplantation.

Seventy-eight days elapsed from the time of the first injection (fig. 2*A*) until the child was discharged from the hospital. At the time of her discharge there was still a small unhealed area on her back (fig. 2*D*). As she was dependent on an indifferent and wholly unreliable parent to fetch her for surgical dressings, these were changed irregularly and were at times wanting. Healing was not complete (fig. 2*E*) until October 22. Therefore, it took one hundred and fifty additional days for the small unhealed area present at the time of her discharge from the hospital to become covered with new skin and epithelium. A total of three hundred and thirty-eight days and three skin transplantations by injection were required for the complete healing of the wound.

(Since the completion of healing of the wound on the patient's back and arms, she has been seen at three to six week intervals in order to observe any changes which might occur in the newly formed skin, particularly in the web formation in the right axilla, which partially binds the arm to the chest wall. This axillary web formation will require plastic repair if full motion of the shoulder is to be restored.)

During the first four months following the child's discharge from the hospital the fibrinous tissue was everywhere excessive beneath the surface of the healed area. Across its lower margin on the back and beneath the upper part of the left arm some keloid formation occurred. Except for a narrow band across the middle of the wound, where healing occurred last and was slowest, there was a noticeable lessening in the amount of subcutaneous fibrinous tissue. The new skin elsewhere gradually became pliable enough to be pinched between the fingers, and at the time of writing its texture feels quite like that of the adjacent undamaged skin. Even though it were to be argued that the newly formed skin is not equal in quality to the skin it has replaced, there can be no denying that it is decidedly unlike a mere cicatrix, a criticism commonly made when thin onlay grafts are used.

During the past few weeks there has been a noticeable decrease in the degree of pigmentation in the small area in the middle of the back (fig. 2*E*) which was the last to heal. It is quite probable that this area may eventually break down or require further surgical attention. The case of this child has thus far been most interesting to observe, and her progress has been comforting to both her attendants and herself.

COMMENT AND SUMMARY

A chronicle of the important contributions to the study and technic of free tissue transplantation is given, and a method for the transplantation of very small particles of skin suspended in saline solution by injecting them beneath the surface of healthy granulation tissue to aid in the healing of an indolent raw surface is again brought to attention.

A striking result recently obtained in an extensive burn of the back and arms of a child is convincing enough to justify presentation of the method for consideration by others.

During the first three or four weeks following the child's accident some improvement was observed from the use of medicaments commonly employed in the treatment of burns, but for the subsequent two and one-half months little if any improvement was noted. One hundred and ten days after the child's admission to the hospital a suspension of finely divided skin was injected into the periphery of the unhealed wound. During the succeeding fifteen days the wound showed more improvement than had occurred in the preceding three and one-half months. Eighteen days after the first injection the procedure was repeated, and again rapid healing was observed for about two weeks. Thereafter, however, healing seemed to diminish with each succeeding change of dressing, so that by the end of the fourth week the healing process had apparently stopped. Thirty-nine days after the second injection the third and last transplantation was done. Three weeks later, when the child was discharged from the hospital, her wound was mostly healed. The lessening of the interim between the second and the third, or last, injection might have further reduced the healing time.

Seventy-eight days elapsed from the time of the first injection until the patient was discharged from the hospital, during which time the major part of the healing occurred.

The small area which was still unhealed when the child was discharged from the hospital took one hundred and fifty days, or *seventy-two days more than was required* for the healing of the major part of the burn, which took place between the time of the first skin transplant and the day of discharge.

When the amount of healing which took place during the seventy-eight days following the first injection is contrasted with the amount of healing which occurred during the one hundred and ten days preceding the first transplantation and also with the one hundred and fifty days following the child's discharge from the hospital, the difference in the rate of healing during these periods is indeed impressive.

The small area where healing occurred last has in recent weeks shown some retrograde change, evidenced by a lessening in the degree of pigmentation. It is probable that this portion of the healed area.

which is mostly scar tissue, may later break down or require further attention. Except for this small area in the middle of the narrow band traversing the back, which on the right side fuses with the web in the axilla, and also where keloid formation is present elsewhere, the newly formed skin possesses none of the characteristics of mere superficial cicatrix. Indeed, most of it is similar in texture to the adjacent undamaged skin.

Time and extensive trial, with careful attention to the details of its application, will be necessary for proper evaluation of this method of skin transplantation. Its advantages over most of the other methods of free skin transplantation are that it can be used when mild surface infection is present; that it is applicable to wounds widely variable in size as well as in location; that it can be used in parts incapable of immobilization, and that the postoperative dressings need be neither so complicated nor, so bothersome.

ACTUAL GROWTH OF YOUNG CARTILAGE TRANSPLANTS IN RABBITS

EXPERIMENTAL STUDIES

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In the field of plastic and reconstructive surgery the transplantation of cartilage has assumed a role of increasing importance. During the past seventy-five years many reports have appeared in the literature describing the experimental and clinical results of the use of cartilage grafts, but the conclusions presented have often been contradictory. At present the evidence for survival of autografts of cartilage is admitted readily, but similar proof for the viability of isografts¹ is not so conclusive. Observations as to whether cartilage grafts were living or dead have depended on the gross and microscopic appearance of apparently viable cartilage cells at the time of removal of the graft. It has been assumed that if a transplant of very young cartilage remains viable in all probability it will resume its regular rate of growth. A demonstrable increase in size of the graft, correlated with the macroscopic and microscopic appearance, would present the clearest evidence for the viability of a transplant and would demonstrate for the first time that young cartilage is capable of continued growth after transplantation. The clinical application of these experiments is limited to the transplantation of cartilage in children. The increasing importance of this measure is discussed later in this paper.

SURVEY OF THE LITERATURE

1. *Experimental Studies on Animal Cartilage Transplantation and Regeneration.*—Interest in the viability and regeneration of cartilage

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1. Throughout the literature with few exceptions there has been an inexact usage of the term homotransplant as defined in American medical dictionaries. To avoid general confusion concerning the exact meaning of the prefix homo- (also homoio- and homeo-), in this report the more precise terms isograft and isograft have been employed to connote the transplantation of tissue to or from a subject of the same species.

dates back to an early period. Both Marchand² and Lexer,³ in their comprehensive surveys on the subject of transplantation of tissues, pointed out that Hippocrates, Celsus and Galen either opposed the idea of any regeneration of cartilage or merely admitted that the healing of cartilage wounds was minimal. Concerning the results obtained by the earliest of modern investigators, it is reported that Dorner⁴ in 1798 and Meckel⁵ and Pauli⁶ in 1815, on the basis of experiments on wound healing in various cartilages, concluded that there was no regeneration of cartilage in incised wounds or open defects. In 1851, however, Redfern,⁷ employing the microscope for the first time to study the healing of wounds in rib and ear cartilage, described an ingrowth of fibrous tissue into the defect and some cartilage cell activity on the edges of the wound; however, they arrived at no definite conclusions. This brief survey of observations on the healing of cartilage wounds brings one to the period when further studies of the viability and regeneration of cartilage were made with the use of free transplants of tissue.

In 1865, Bert,⁸ observing the vascularization of the tail of a rat which had been buried beneath the skin as a free transplant, noticed that the nerve and muscle tissue degenerated early but that the bone tendon and the cartilage remained viable for months. If absorption took place under abnormal conditions, the remnants of the graft were the calcified articular cartilages. Although he did not employ cartilage as a separate graft, this investigator is generally accredited with being the first to report the presence of living cartilage after free transplantation. Free cartilage grafts had been studied previously (in 1852) by Middeldorf,⁹ but he reported complete absorption of all grafts.

Ollier¹⁰ (1867) was the first investigator to declare that cartilage requires the presence of its perichondrium for successful transplantation. Working with rabbits and fowl, he found the cartilage transplants

2. Marchand, F.: *Der Process der Wundheilung mit Einschluss der Transplantation*, in Billroth, T., and Luecke, A.: *Deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1901, no. 16.

3. Rehn, E., and Ruef, H.: *Die freie Knorpeltransplantation*, in Lexer, E.: *Die freie Transplantationen*, in von Bruns, P.: *Neue deutsche Chirurgie*, Stuttgart, Ferdinand Enke, 1924, vol. 2, pp. 286-369.

4. Dorner, cited by Rehn and Ruef.³

5. Meckel, cited by Rehn and Ruef.³

6. Pauli, cited by Marchand.²

7. Redfern, cited by Lefas²⁰ and Rehn and Ruef.³

8. Bert, P.: *Sur la greffe animale*, *Compt. rend. Acad. d. sc.* **61**:587, 1865.

9. Middeldorf, cited by Rehn and Ruef.³

10. Ollier, L.: *Traité expérimental et clinique de la régénération des os et de la production artificielle du tissu osseux*, Paris, V. Masson & fils, 1867, vol. 1, p. 162.

viable after 3 months. Wounds in the articular cartilage of young rabbits healed, but similar wounds in adult rabbits showed no repair. Many of the smaller cartilage grafts in dogs and in fowl were absorbed, however. Likewise, in 1878 Tizzoni¹¹ described fatty degeneration occurring in cartilage cells after a few days of implantation and the disappearance of the grafts in the granulation tissue which enveloped them.

Zahn¹² in 1877 reported similar failures with small pieces of adult rib cartilage grafts, regardless of the locality to which the grafts were transplanted. In later trials with fetal cartilage, however, he observed definite growth, with activity limited to the cells on the periphery; the greatest increase in size occurred where the blood supply was best. Leopold¹³ in 1881 demonstrated a luxuriant development of fetal cartilage transplants placed in the abdomen, in the jugular vein or in the anterior chamber of the eye. In some instances fetal grafts increased in size over three hundred fold during a period of 200 days. Because he was unable to observe any growth in transplants of non-fetal cartilage in rabbits, he concluded that ordinary cartilage grafts remained stationary, shrank or eventually were absorbed, whereas fetal cartilage grafts always grew, even as heterotransplants. In the same year (1881), one other investigator, Gies,¹⁴ reported no healing of cartilage defects on joint surfaces in clean wounds after 150 days.

Prudden¹⁵ (1881), in a carefully controlled series of experiments, supplied further proof that living cartilage can be transplanted successfully. He placed 200 small fragments of hyaline cartilage from the head of the femur and the chondral section of the ribs of a freshly killed rabbit into the subcutaneous tissues of a living rabbit, and evaluated his results by studying over 1,200 microscopic slides of sections removed at intervals varying up to 399 days. Among other conclusions, he emphasized that transplanted cartilage may live for many months and that cells may change their shape and size, entering into the formation of embryonal cartilage or taking an active part in the formation of new connective tissue. Because these bits of cartilage were taken with the greatest care to exclude any perichondrium, it was indicated for the first time that cartilage transplants may survive without attached perichondrium.

11. Tizzoni, G.: *Sulla istologia normale e patologica delle cartilagini ialine*. Arch. per le sc. med. 2:27, 1877-1878.

12. Zahn, F. W.: *Sur le sort des tissus implantés dans l'organisme*, Congr. méd. internat. de Genève, 1877, p. 658.

13. Leopold, G.: *Experimentelle Untersuchungen über die Aetiologie der Geschwülste*, Virchows Arch. f. path. Anat. 85:283, 1881.

14. Gies, T.: *Ueber Heilung von Knorpelwunden*, Arch. f. klin. Chir. 26: 848, 1881.

15. Prudden, T. M.: *Experimental Studies on the Transplantation of Cartilage*, Am. J. M. Sc. 82:360, 1881.

Diametrically opposed to this observation were the results of Fischer's¹⁶ work on costal cartilage (1882), which led him to support Ollier's¹⁰ original contention that transplants without perichondrium would not survive. After showing transitory cellular growth, cartilage grafts without perichondrium always degenerated in about 8 weeks, he found, but costal cartilage with its perichondrium intact showed no alteration in structure. One of his most valuable contributions was the observation that the younger the cartilage transplant the greater is its power of regeneration and its innate viability. Likewise, his research on fetal cartilage transplants substantiated the findings of previous investigators (Zahn;¹² Leopold¹³) in the demonstration of tremendous growth possibilities of this tissue.

By this time it was fairly well established that with a favorable environment and the use of a careful technic cartilage transplants will survive. Later investigations have verified Prudden's¹⁵ original observation that grafts of cartilage denuded of their perichondrial coverings will remain viable. At this point it becomes increasingly difficult to untangle the maze of contradictory results; so an effort is made to relate only the general trend of modern investigation on this subject by giving a few details of the more important contributions.

Von Mangoldt¹⁷ in 1899 gave both experimental and clinical evidence that transplanted cartilage survived for periods up to 19 months. Von Helferich¹⁸ (1899) claimed rather poor results from his work with epiphysial cartilage transplants in rabbits, while Enderlen¹⁹ reported in the same year that reimplanted epiphysial cartilage displayed remarkable viability. Lefas²⁰ in 1902 affirmed that no real repair was evident in articular cartilage wounds, while Pennisi,²¹ two years later, demonstrated definite areas of cartilaginous proliferation beyond the area of necrotic cells along the edge of the wound. On the basis of contributions by Marchand² verifying the findings of Pennisi²¹ and others, it appears that some regenerative power in cartilage is being recognized, and these investigations emphasize not only the transplantability of cartilage but the possibility of actual growth.

16. Fischer, E.: Ueber Transplantation von organischen Materiel, Deutsche Ztschr. f. Chir. **17**:362, 1882.

17. von Mangoldt, F.: Ueber die Einpflanzung von Rippenknorpel in den Kehlkopf zur Heilung schwerer Stenosen und Defecte, Verhandl. d. deutsch. Gesellsch. f. Chir., 1899, p. 613.

18. von Helferich: Versuche über die Transplantation des Intermediärknorpels wachsender Röhrenknochen, Deutsche Ztschr. f. Chir. **51**:564, 1899.

19. Enderlen: Zur Reimplantation des resecirten Intermediärknorpels beim Kaninchen, Deutsche Ztschr. f. Chir. **51**:574, 1899.

20. Lefas, E.: Sur la réparation du cartilage articulaire, Arch. de méd. expér. et d'anat. path. **14**:378, 1902.

21. Pennisi, A.: Sul processo di guarigione delle ferite delle cartilagini, Policlinico (sez. chir.) **11**:489, 1904.

Seggel²² in 1904 found degeneration in most of his adult cartilage grafts, while Judet²³ pointed out that transplants survive best in young animals. As the result of his experiments, Axhausen²⁴ in 1912 concluded that the transplantation of joint cartilage as an isograft has the greatest practical application.

Davis²⁵ (1913) placed large pieces of rib cartilage in pedunculated flaps on dogs, and the cartilage remained viable with no evidence of absorption or degeneration either macroscopically or microscopically. The grafts shrank little, if at all, during a period of 4 months; apparently they were receiving nourishment and were not being tolerated merely as foreign bodies. Four years later the same author, working on free grafts of cartilage and bone,²⁶ showed that cartilage lived for 582 days, while bone was almost completely absorbed. There were no evidences of absorption in the cartilage grafts, although the sharp edges had become smooth, and the microscopic picture showed normal living cartilage of good staining quality with some central calcification and slight absorption. Davis asserted clearly that the presence or absence of the perichondrium seemed to have little effect on the nourishment of the cartilage cells.

Nageotte²⁷ in 1917 described proliferation of new cartilage cells along the edges of wounds in living cartilage, and Nussbaum²⁸ in the following year found that free transplants of cartilage might show absorption of the older cartilage cells by an ingrowth of young cells from the perichondrium without the aid of lymphocytes or blood vessels. In correlating his own experimental observations with an extensive survey of the existing literature, Lexer³ (1925) concluded that hyaline cartilage (rib and joint) has a marked ability to survive as a living transplant.

More recently, Mannheim and Zypkin²⁹ studied autogenous cartilage grafts in rabbits for a year and similar transplants in dogs for 30

22. Seggel, R.: Verhalten des Knorpels bei Uebertragung in die freie Bauchhöhle, Deutsche Ztschr. f. Chir. **75**:326, 1904.

23. Judet, cited by Rehn and Ruef.³

24. Axhausen, G.: Ueber den histologischen Vorgang bei der Transplantation von gelenkenden, insbesondere über die Transplantationsfähigkeit von Gelenkknorpel und Epiphysenknorpel, Arch. f. klin. Chir. **99**:1, 1912.

25. Davis, J. S.: Transplantation of Rib Cartilage into Pedunculated Skin Flaps: An Experimental Study, Bull. Johns Hopkins Hosp. **24**:116, 1913.

26. Davis, J. S.: A Comparison of the Performance of Free Transplants of Bone and Cartilage: An Experimental Study, Ann. Surg. **65**:170, 1917.

27. Nageotte, J.: L'organisation de la matière dans ses rapports avec la vie. Paris, Félix Alcan, 1922, p. 96.

28. Nussbaum: Ueber Epithel- und Knorpeltransplantation bei Trachealfekten, Beitr. z. klin. Chir. **110**:101, 1918.

29. Mannheim, A., and Zypkin, B.: Ueber freie autoplastische Knorpeltransplantation, Arch. f. klin. Chir. **141**:668, 1926; abstracted, J. A. M. A. **87**:2132 (Dec. 18) 1926.

months.³⁰ They concluded that (a) grafts placed in the subcutaneous tissues showed a reduction in thickness of the perichondrium with some evident cellular destruction and replacement by fibrous tissue; (b) the cartilage transplants buried in muscle were in the finest state of preservation, while those placed in the skull were inferior to grafts in the subcutaneous tissues, and (c) partial removal of the perichondrium increased the viability of a cartilage graft—a completely new idea.

Loeb³¹ in 1926 and 1927 added further knowledge to the subject of cartilage transplantation by presenting a most interesting series of investigations, which was supplemented in 1935 by an article by Loeb and Siebert.³² In the guinea pig, autografts of cartilage were usually preserved *in toto*, with an occasional minor tissue reaction observed after periods varying up to 5½ months. Isografts always provoked a distinct lymphocytic reaction, a marked increase in connective tissue and increased destruction of the cartilage by invading lymphocytes and fibrocytes. In another experiment on rats Loeb established a definite correlation between the genetic relation of the donor with the host and the severity of tissue reaction on the part of the host against implants. Thus, in "syngenesiotransplantation" there was less reaction on the part of the host tissues to grafts of close familial and genetic origin. As conclusive proof that transplanted cartilage can survive for long periods, serial transplantation of a piece of cartilage was carried on in rats for over 6 years, which is twice the normal life span. Loeb concluded that cartilage, in comparison with other tissues, exhibits greater viability in transplantation because of (a) a diminution in the homoiotoxic, or isotoxic, reaction on the part of the host tissues toward cartilage; (b) a greater resistance of cartilage (because of its hyaline substance) toward the instruments of attack (lymphocytes and connective tissue cells), and (c) the lower tissue metabolism of cartilage, which favors survival until nourishment is established for the graft.

In a more recent paper, Borst³³ (1928) maintained that the regeneration of cartilage depends on the perichondrium, although denuded cartilage can remain alive after transplantation. Gorbunoff³⁴ found

30. Mannheim, A., and Zypkin, B.: Späteresultate der Knorpelplastik, Arch. f. klin. Chir. **149**:31, 1927.

31. Loeb, L.: Autotransplantation and Homoiotransplantation of Cartilage in the Guinea Pig, Am. J. Path. **2**:111, 1926; Autotransplantation and Homoiotransplantation of Cartilage and Bone in the Rat, *ibid.* **2**:315, 1926; Transplantation and Potential Immortality of Mammalian Tissues, J. Gen. Physiol. **8**:417, 1926; Syngenesiotransplantation in the Rat, Am. J. Path. **3**:45, 1927.

32. Loeb, L., and Siebert, W. J.: Transplantation of Skin and Cartilage in Chickens, Arch. Path. **20**:28 (July) 1935.

33. Borst, M.: Das pathologische Wachstum, in Aschoff, L.: Pathologische Anatomie, ed. 1, Jena, Gustav Fischer, 1928, p. 611.

34. Gorbunoff, W. P.: Vergleichende Studien über die Knochen- und Knorpel-Auto- und Homotransplantation, Arch. f. klin. Chir. **161**:651, 1930.

that his isografts resisted absorption nearly as well as autotransplants. Finally, Fohl³⁵ (1929) and Pereira and Dupertuis³⁶ (1936) determined that fresh autografts of epiphyseal cartilage survived, even to the extent of producing typical bony exostoses.³⁶

Therefore, on the basis of this survey one may conclude: (a) that fresh animal cartilage with or without its perichondrium will survive as a viable autotransplant or isotransplant for many months; (b) that isografts cause a greater cellular response on the part of the host tissues and exhibit more evidence of destruction and invasion by fibrous tissue; (c) that under favorable circumstances cartilage demonstrates some regenerative power, which is closely associated with the presence of its perichondrium, and (d) that young cartilage retains its viability better than does adult tissue and survives best in host tissues with the greatest vascularity.

2. *Heterotransplantation*.—Almost universally, investigators agree that the heterotransplantation of tissues is doomed to failure. On this subject, Lexer³ emphasized that a heterograft of joint or rib cartilage with or without its perichondrium absorbs completely in a few months. In 1916, Imbert³⁷ and his co-workers used young beef cartilage from the scapula to fill in cranial defects and found that connective tissue adhesions permitted its temporary survival. He made the observation that the progressive attack and absorption are a biologic process since the heterograft was not ejected as a dead sequestrum. Likewise, Loeb³⁸ demonstrated that the injurious body fluid action of the host is strongest against heterografts and that even dead heterogenous tissue may evoke this marked tissue reaction.

3. *Use of Dead or Preserved Cartilage for Grafts*.—Recently there has been a revival of interest in the clinical possibilities of preserved cartilage ultimately replacing autogenous grafts. The first animal experiments were carried out fifty-nine years ago, by Prudden,¹⁵ who reported complete absorption of all grafts after fixation by 95 per cent alcohol, phenol, electric desiccation, burning, boiling or drying. Seggel²² in 1904 noted early destruction of his alcohol-preserved grafts, but Regoli³⁹ (1922) decided that preserved tissue might prove useful

35. Fohl, T.: Weitere Versuche über die Transplantation der Knorpelfuge. Arch. f. klin. Chir. **155**:232, 1929.

36. Pereira, S., and Dupertuis, S. M.: Recherches expérimentales sur la pathogénie des exostoses ostéogéniques à l'aide de greffes de cartilage de conjugaison, Presse méd. **44**:162 (Jan. 25) 1936.

37. Imbert, L.; L'Heureux, C., and Rouslacroix: Recherches sur les greffes cartilagineux hétéroplastiques, Rev. de chir. **52**:111, 1916.

38. Loeb, L., and Harter, J. S.: Heterotransplantation of Cartilage and Fat Tissue and the Reaction Against Heterotransplants in General, Am. J. Path. **2**:521, 1926.

39. Regoli, G.: Innesti di tessuti morti fissati e conservati, Policlinico (sez. chir.) **29**:559, 1922.

because "neocartilage" appeared as a substitute for the dead cartilage, which in itself never became revived. Nageotte,⁴⁰ on the other hand, discovered that alcohol-preserved cartilage grafts were rapidly fragmented by the invasion of connective tissue cells and appeared to exert a specific action favoring the transformation of connective tissue into bone rather than new cartilage cells. Employing similar methods of fixation, Poletti⁴¹ (1923), Nigrisoli⁴² (1927) and Didier and Guyon⁴³ (1928) described invasion and absorption of these grafts with occasional formation of "neocartilage" or bone.

Considering the clinical possibilities of preserved cartilage, Gorbunoff³⁴ noted experimentally that his fresh cartilage autotransplants showed a greater decrease in size through absorption than did the preserved grafts during the same period. On the basis of this observation and of the recognized ability of preserved cartilage to be replaced by firm, living connective tissue, this author predicted that preserved transplants probably will replace autoplasmic and alloplastic materials. A clinical report on the use of cartilage preserved in physiologic solution of sodium chloride and merthiolate (4:1) appeared in 1938 (O'Connor and Pierce⁴⁴). These workers found that preserved cartilage isografts at times provoked slightly more local tissue reaction than did fresh autografts but showed less tendency to bend and curl. After five years in this series of 375 grafts no absorption had occurred; the grafts had shown a conspicuous ability to resist infection, and in each case (except 6 cases of infection) the transplants had retained their original size and identity. More recently Peer⁴⁵ has reported the progressive invasion and partial absorption of alcohol-preserved human rib and septal cartilage grafts after periods varying up to 2 years. He observed no destruction or invasion by fibrous tissue in fresh autografts up to 6 years and therefore concluded: "Autogenous rib cartilage is better material for plastic repair than dead, pickled cartilage." Finally,

40. Nageotte, J.: Escarre par dessiccation du cartilage auriculaire vivant et des portions dénudées de greffes cartilagineuses mortes; mode d'élimination et phénomènes consécutifs, *Compt. rend. Soc. de biol.* **80**:689, 1917.

41. Poletti, B.: Su neoformazioni cartilaginee ed ossee determinate da innesti di frammenti di cartilagine e d'osso fissati, *Arch. ital. di chir.* **6**:179, 1922; abstracted, *J. A. M. A.* **80**:360 (Feb. 3) 1923.

42. Nigrisoli, P.: Esperimenti di innesto di cartilagine fissata nel rene e di sostituzione di parti scheletriche con cartilagine fissata, *Arch. per le sc. med.* **49**:689, 1927.

43. Didier, R., and Guyon, L.: Production de cartilage et d'os, au sein de greffes vivantes et mortes, chez le lapin, *Compt. rend. Soc. de biol.* **98**:443, 1928.

44. O'Connor, G. B., and Pierce, G. W.: Refrigerated Cartilage Isografts, *Surg., Gynec. & Obst.* **67**:796, 1938.

45. Peer, L. A.: (a) Experiments on Alcohol Preserved Cartilage in Humans. *Arch. Otolaryng.* **27**:42 (Jan.) 1938; (b) Fate of Living and Dead Cartilage Transplanted in Humans, *Surg., Gynec. & Obst.* **68**:603, 1939.

Brown⁴⁶ in 1940 presented his experiences in the clinical use of preserved cartilage and expressed the opinion that it should be regarded as a second choice substitution when a fresh autograft or isograft is not advisable.

It appears from this experimental evidence that preserved cartilage grafts undergo absorption and may be replaced eventually by fibrous tissue. Clinical reports have been more encouraging, and in many cases these grafts may prove satisfactory, but when permanent support is desired it is dubious whether preserved grafts will replace fresh autotransplants.

4. *Actual Growth of Cartilage Transplants.*—A search through the literature has failed to reveal any experimental data relating to a measurable increase in size occurring in a living graft of young permanent cartilage. Earlier investigators have reported that young cartilage has a greater viability than adult tissue, but the possibility of true growth after transplantation has not been advanced. For the most part statements regarding growth have been negative, and frequently there has been an inexact use of this term to denote survival or viability of the graft. The only experimental background for these studies on the actual growth of young cartilage transplants, therefore, consists of sporadic statements throughout the literature.

One of the most interesting observations on this subject was offered by Bert⁸ in his original paper in 1865. He discovered that the denuded tail of a rat when implanted beneath the skin as a free graft kept pace with the rest of the animal in the matter of growth but never grew larger than normal. Two years later, Ollier¹⁰ grafted different types of cartilage in very young dogs; rapid absorption (but never any growth) occurred in all transplants. It is to be noted that Zahn,¹² Leopold,¹³ Fischer¹⁶ and von Heflerich¹⁸ reported vigorous growth of fetal cartilage under varying conditions of implantation but never any evidence of growth in nonembryonal cartilage transplants. In 1924, Lexer,⁹ in his comprehensive survey of a great number of experiments on cartilage transplantation, established that no increase in volume from expansion or swelling occurred; any changes in such grafts were regressive rather than progressive. Various authors⁴⁷ have reported actual growth in epiphyseal cartilage transplants, often with the ultimate formation of bone, but grafts of temporary cartilage hardly enter the scope of this study. Finally, in the modern literature, Davis,²⁵ Didier and Guyon⁴³ and Peer^{45b} did not observe any increase in the size of their grafts.

46. Brown, J. B.: Preserved and Fresh Homotransplants of Cartilage, *Surg. Gynec. & Obst.* 70:1079, 1940.

47. Seggl.²² Fohl.³⁵ Pereira and Dupertuis.³⁶

The paucity of experimental observations on the possible growth of cartilage after transplantation is probably the result of two factors: (a) the fact that the large majority of investigators employed adult cartilage and (b) the fact that this phase of cartilage transplantation has a more limited clinical and practical application.

EXPERIMENTAL STUDIES ON THE GROWTH OF YOUNG CARTILAGE TRANSPLANTS

Plan, Material and Method.—The object of this investigation was to study the growth of young permanent cartilage when transplanted under various conditions. The rabbit appeared to be the animal best suited for this purpose, because

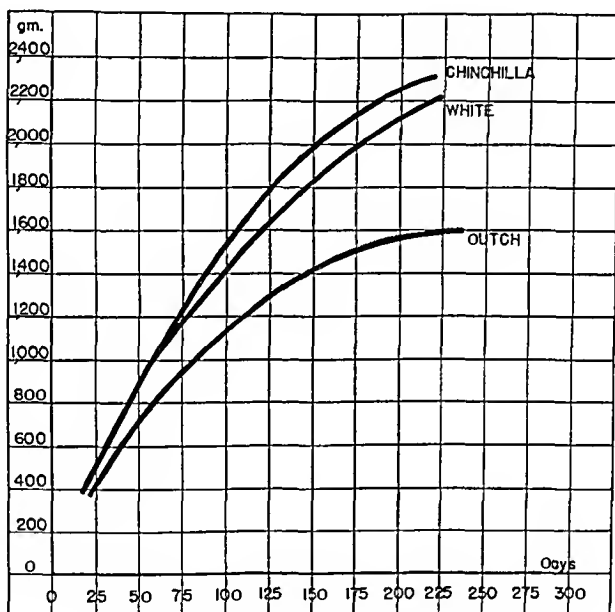


Fig. 1.—Normal weight curves.

the ear affords a generous supply of material and in the very young is still of sufficient size to allow grafts of measurable area to be obtained. The rabbit ear enlarges rapidly in the first few months of life, and the rate of growth is greater than the corresponding increase in weight (figs. 1 and 2). With ordinary precautions infection seldom occurred, and the baby rabbits tolerated the operative procedures exceedingly well.

Three different strains of rabbits were used in these experiments. The chinchilla, or gray, variety and the pure white strain are larger and show grossly a greater increase in the size of the ear during growth (fig. 2). The Dutch, or black and white, breed tolerates all experimental procedures well but is smaller and shows less growth over a given period. These different breeds were employed simultaneously in some of the trials with isografts to eliminate the factor of close genetic relationship.

In all, 107 separate cartilage grafts were observed for periods varying up to 253 days. In order to obtain comparable conditions for growth, several transplants were placed in the same animal. Twenty-six rabbits between the ages of 12 and 24 days were selected; 2 died immediately after operation as the result of an overdose of the anesthetic. Several died after two or three months from inter-current disease, but their grafts were included in the final results. Feeding problems were of minor importance, because the mother accepted the young rabbits back into the litter, and in every case they nursed well.

A careful record was kept of the weight of each animal before operation and at the time of examination of the specimen. Only one ear was used as a donor site for cartilage, which permitted measurements of length on the alternate side to be utilized as an accurate control. Many of the grafts were held in place

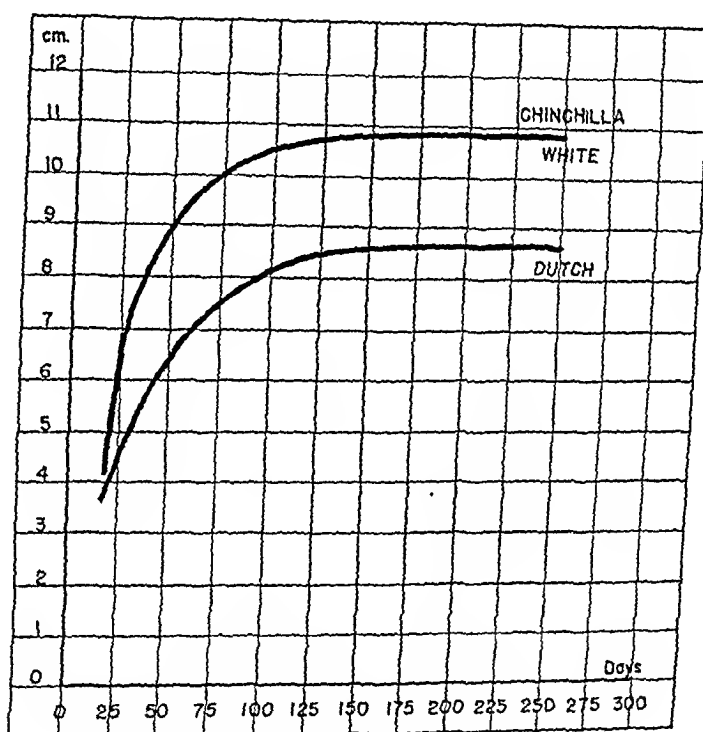


Fig. 2.—Growth curves of control ears.

with fine silk sutures, which also served as markers. This did not introduce a variable factor, for the microscopic sections showed only the slightest localized foreign body reaction, with an occasional giant cell.

Technic.—Each transplantation was performed with the utmost surgical precision. Preparation of the skin consisted of shaving, cleansing with soap and water and application of tincture of iodine. Excess iodine was sponged off carefully with alcohol, and each area was draped with sterile towels. Mosquito hemostats, fine forceps, small curved scissors and regulation eye needles allowed a careful, gentle technic to be employed. Each wound was closed, in layers when necessary, by interrupted sutures of B-Deknatel braided silk. Careful hemostasis and accurate approximation of the edges of the skin were carried out, so no dressings were necessary. On the seventh day the remaining skin sutures were removed, and in the entire series only 2 grafts were extruded from infected wounds. The transplants were kept in a sponge moistened with saline solution.

while closure of the donor site and preparation of the recipient bed were carried out. The time required for this averaged fifteen to thirty minutes for the autografts and up to forty-five minutes for the isografts.

When this problem was planned, the question of anesthesia for these very young rabbits presented some difficulties. The margin of safety with ether or with any of the various intraperitoneal drugs was considered too small to permit their use. Local infiltration with procaine hydrochloride solution proved to be the practical answer to this problem. Clinically, local anesthesia has had no deleterious effects on transplants; as it was used successfully in each experiment, no variable factor was introduced. The rabbits submitted to the injection without struggle or manifest pain and lay quietly, tied in place, for operations lasting an hour or

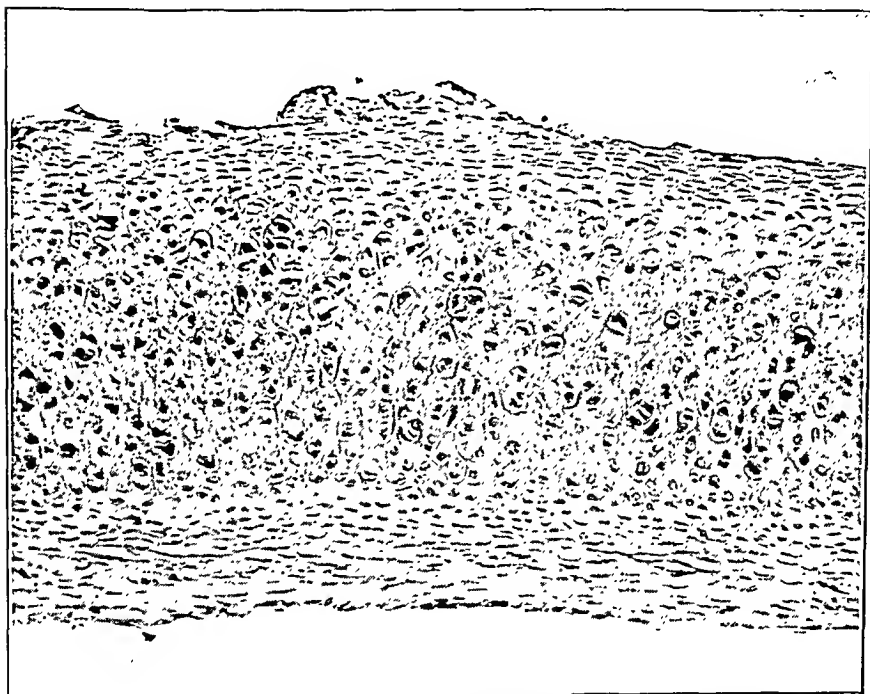


Fig. 3.—Cross section of normal ear cartilage in a 21 day old rabbit. Compare with figure 4.

more. Two rabbits died within forty-eight hours of operation, seemingly from the toxic effects of about 5 cc. of 1 per cent procaine hydrochloride. A solution of 0.5 per cent with 10 drops of epinephrine hydrochloride solution (1:1,000) added to each ounce (30 cc.), for hemostatic purposes, proved safe when injected in quantities of 2 to 3 cc.

The microscopic sections were fixed in Bouin's solution and stained with hematoxylin and eosin. Acid orcein stain was used to identify elastic fibrils in ear cartilage, and the trichrome method was employed to differentiate connective tissue in selected sections.

Series 1: Autotransplants of Ear Cartilage in Young Rabbits.—Procedure: In rabbits 14 to 21 days old (average age, 17.6 days), 9 separate measured pieces

TABLE 1.—Results in First Series

Position of Graft	Number and Breed of Rabbit	Age at Operation, Days	Duration of Experiment, Days	Weight, Gm.		Ear Length, Cm.		Per Cent Increase in Ear Length	Size of Graft, Cm.		Per Cent Increase in Length of Graft	Per Cent Increase in Area of Graft
				Operation	Autopsy	Operation	Autopsy		Operation	Autopsy		
Subcutaneous.....	301 (Chinese)	17	85	325	1,300	5.0	11.5	130	0.6 × 0.35	1.5 × 0.9	150	542
Muscle.....	301 (Chinese)	17	85	330	1,300	5.0	11.5	130	0.7 × 0.3	1.8 × 0.9	157	671
Subcutaneous.....	302 (Chinese)	17	71	180	855	4.2	10.0	138	0.6 × 0.5	1.3 × 0.7	117	203
Muscle.....	302 (Chinese)	17	71	180	855	4.2	10.0	140	0.6 × 0.5	1.5 × 1.0	150	400
Subcutaneous.....	317 (Dutch)	14	253	225	1,500	3.5	9.1	56	0.6 × 0.4	1.3 × 0.9	117	338
Muscle.....	318 (White)	18	253	225	1,500	3.5	9.1	56	0.6 × 0.5	1.7 × 1.4	183	672
Subcutaneous.....	311 (Chinese)	20	22	305	880	5.9	10.8	73	5.7 × 1.5	6.0 × 1.75	5	27
Muscle.....	312 (Chinese)	20	22	305	880	5.9	10.8	73	4.5 × 1.7	5.9 × 2.6	31	100
Subcutaneous.....	308 (Chinese)	16	137	385	1,905	5.9	9.2	108	3.8 × 1.4	5.0 × 2.5	33	135
Muscle.....	305 (Chinese)	16	223	230	2,235	6.8	9.2	102	2.3 × 2.0	6.5 × 3.7	183	422
Subcutaneous.....	305 (Chinese)	21	222	230	2,235	4.1	11.0	102	2.2 × 1.7	5.3 × 4.5	141	537
Muscle.....	306 (Chinese)	21	222	185	2,320	4.0	10.0	125	0.8 × 0.5	2.1 × 1.5	163	688
Subcutaneous.....	306 (Chinese)	21	30	240	2,350	4.2	11.0	125	0.85 × 0.4	2.6 × 1.1	208	1,070
Muscle.....	317 (Dutch)	14	253	240	4.3	9.7	127	1.4 × 0.8	1.8 × 0.9	80	124
Subcutaneous.....	318 (White)	18	253	225	4.3	9.7	127	1.0 × 0.45	1.1 × 0.6	175	560
Muscle.....	4 grafts	18	285	285	1,500	3.5	9.7	114	0.4 × 0.25	1.4 × 0.7	110	171
Subcutaneous.....	4 grafts	16	253	2,100	4.8	10.8	130	0.05 × 0.5	132	443
Muscle.....	4 grafts	19	101	130	147	453
Subcutaneous.....	4 grafts	19	104	130	148	600
Muscle.....	4 grafts	19	104	130	124	389

of fresh ear cartilage were implanted into subcutaneous pockets on the back of the same animal. Prompt healing of the wounds followed in each case, and the grafts were examined at varying intervals up to 253 days. As a general rule these grafts remained flat under the skin and could be palpated and seen rather easily. In 4 animals of this group similar grafts were buried in the posterior muscles of the thigh for a comparison of the development of the transplant in a more vascular bed. In 4 other rabbits small portions of ear cartilage were removed, measured and sutured back into place; these were to demonstrate the reaction of free grafts when returned to their own environment.

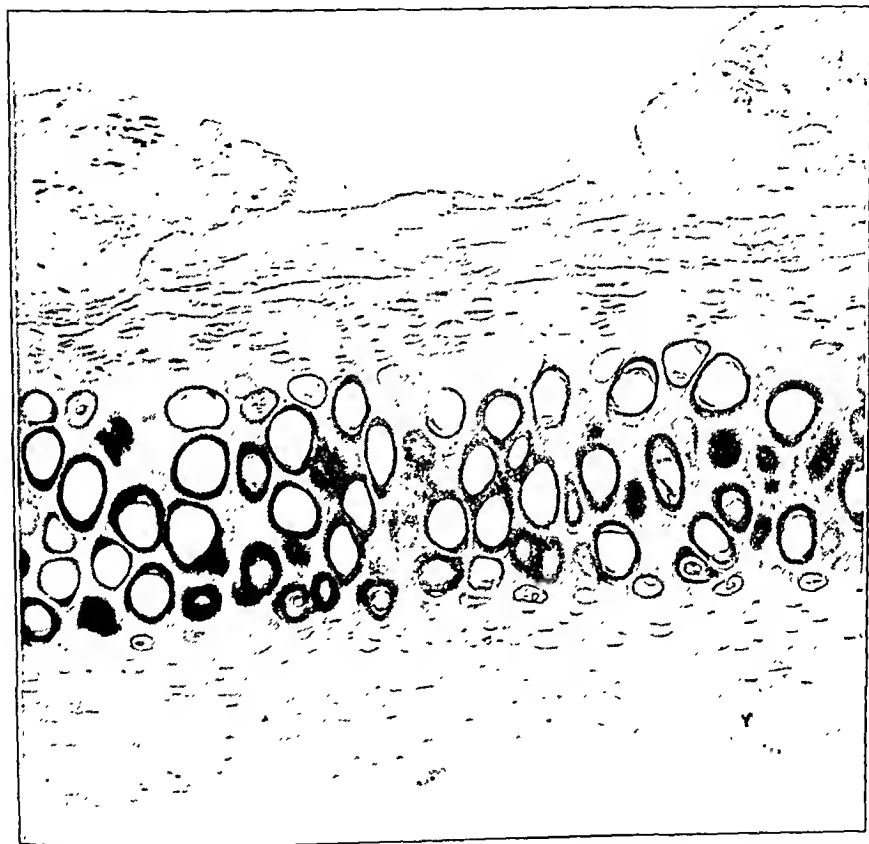


Fig. 4.—Cross section of normal ear cartilage in an adult rabbit. For comparison, the photomicrograph of young cartilage in figure 3 is of the same magnification.

Results: During an average growth period of 140 days, each of the aforementioned 17 autotransplants from rabbits 2 to 3 weeks old exhibited a measurable increase in size. During the same period the control ear increased its length by 128 per cent, while an average of the measured length of the grafts at the time of examination showed an increase of 122 per cent. (The transplants were taken with the longer side always in the long axis of the ear.) The average increase in surface area was 413 per cent, whereas roughly the increase in surface

area of the control ear (calculated by taking the square of the increase in ear length) was 419 per cent.

In the 4 animals in which similar grafts were buried beneath the skin and in the thigh muscles of the same rabbit for comparison, a considerably greater increase in size was found in each of the latter group. During an average period of 104 days for these 4 animals the subcutaneous grafts averaged an increase in length of 124 per cent, as compared with 148 per cent for those implanted in muscle; as for the average increase in area, the ratio was 389 per cent to 600 per cent for the muscle group.

When the cartilage graft was replaced in its donor site in the ear, the average increase in length of 147 per cent indicated additional growth over the general average. As for area, the result of 453 per cent gain is close to the

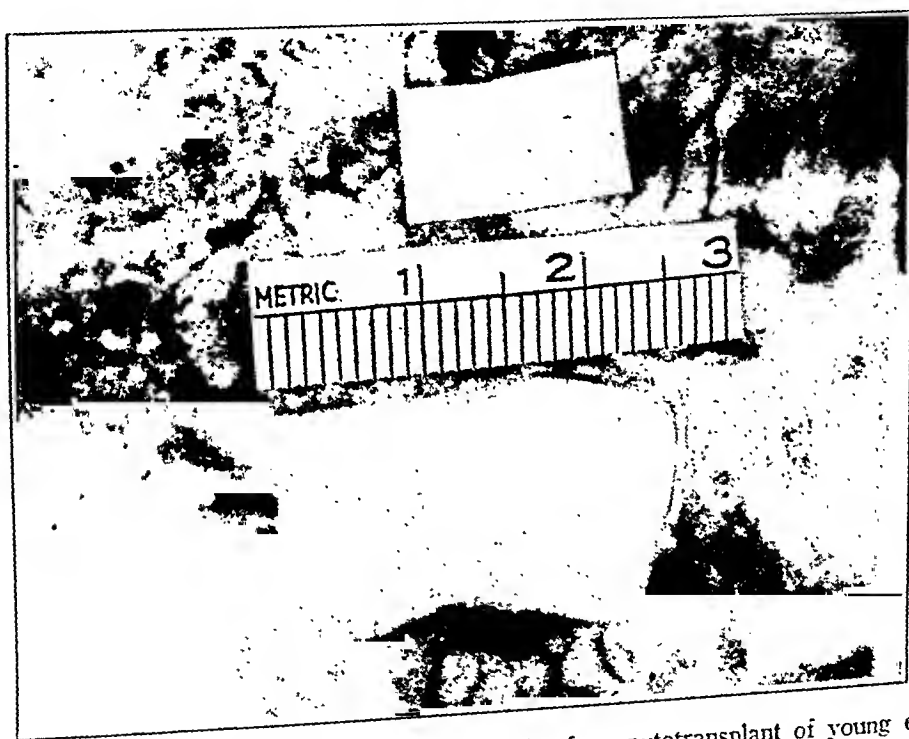


Fig. 5 (rabbit 306, series 1).—Photograph of an autotransplant of young ear cartilage still adherent to the under surface of the skin of the back. The piece of paper immediately above the metric scale shows the size of the graft before transplantation. There were 65 per cent increase in length and 124 per cent increase in area during a period of 39 days.

general average but well below the muscle group, even though these grafts were undisturbed for a much longer period (253 days).

Microscopic Observations: All transplants gave microscopic confirmation of the presence of living, growing cartilage. The intercellular substance stained well with the basophilic dye, and the cells appeared viable. In the older specimens the cartilage became less cellular, approaching typical adult cartilage in appearance, and the perichondrium was thinner and less active, but intact. In all the slides fibrous tissue could be seen about the grafts, but there was no suggestion of active penetration by it. The amount of connective tissue present was variable but not excessive, and about an occasional silk suture was found a small localized reaction with a few giant cells.

Each of the grafts gave indication of growth by apposition at the ends. Here the perichondrium had developed around the free edge, and younger transitional cartilage cells surrounded by paler-staining matrix were in evidence (fig. 6). Only one localized area of degeneration could be distinguished in this series, and no calcification, absorption or bone formation was present.

In only one of the implants into muscle was there microscopic evidence of increased growth activity on the free edge. In another of this group a blood vessel was identified in the perichondrium (fig. 7). Of the 4 animals in which the grafts were replaced in the ear, all had fibrous bridging of the defect between

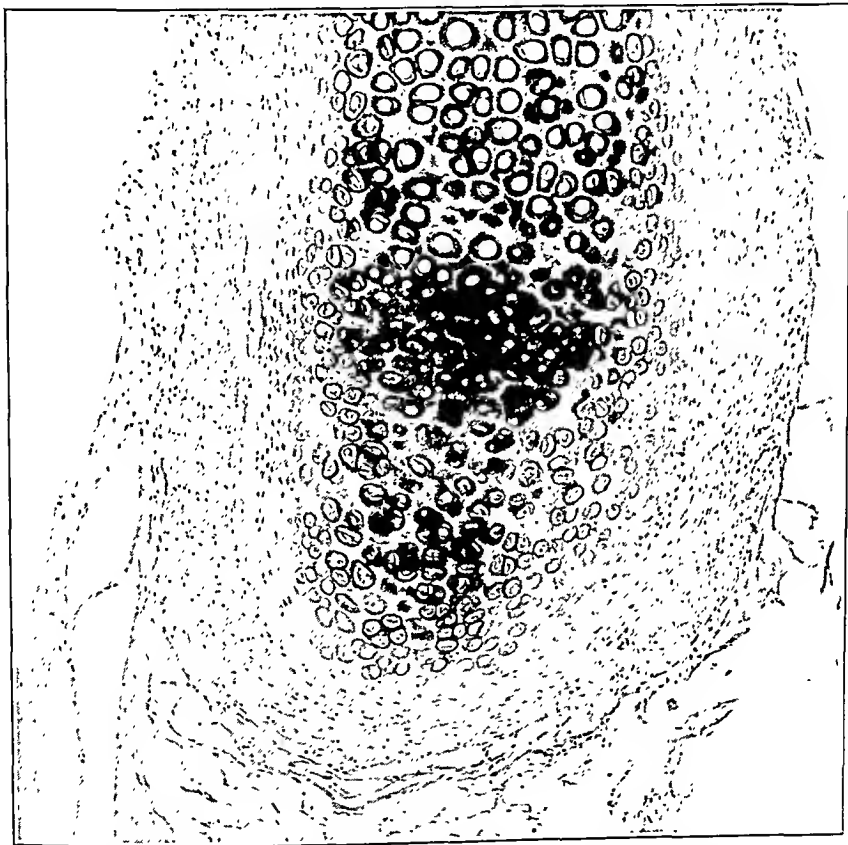


Fig. 6 (rabbit 300, series 1).—Photomicrographic cross section of one edge of a young ear cartilage autograft which had been placed beneath the skin for 128 days. The proliferation of young cartilage cells is apparent about the lower portion of the cartilaginous plate. (Compare with figure 10.)

the implant and the adjacent normal ear cartilage; often proliferative activity was apparent about these areas, but no complete bridge of cartilage tissue was present. Elastic fibrils in the matrix substance were difficult to identify in the routine sections but could be recognized easily when special staining methods were used.

In the original plan of experiment observation of the role of the perichondrium in growth was included. Actually this proved impractical, because the control

sections of ear cartilage from which the perichondrium presumably had been denuded still showed portions attached to the graft. The cartilage plate in these young rabbits was so thin and fragile that more vigorous efforts to remove the perichondrium were futile. Macroscopically one of the implants returned to the original site in the ear showed less growth than the control ear. In this case the normal ear cartilage adjacent to the implant had wrinkled; seemingly it was retarded in its normal development by fibrous adhesions to the graft.

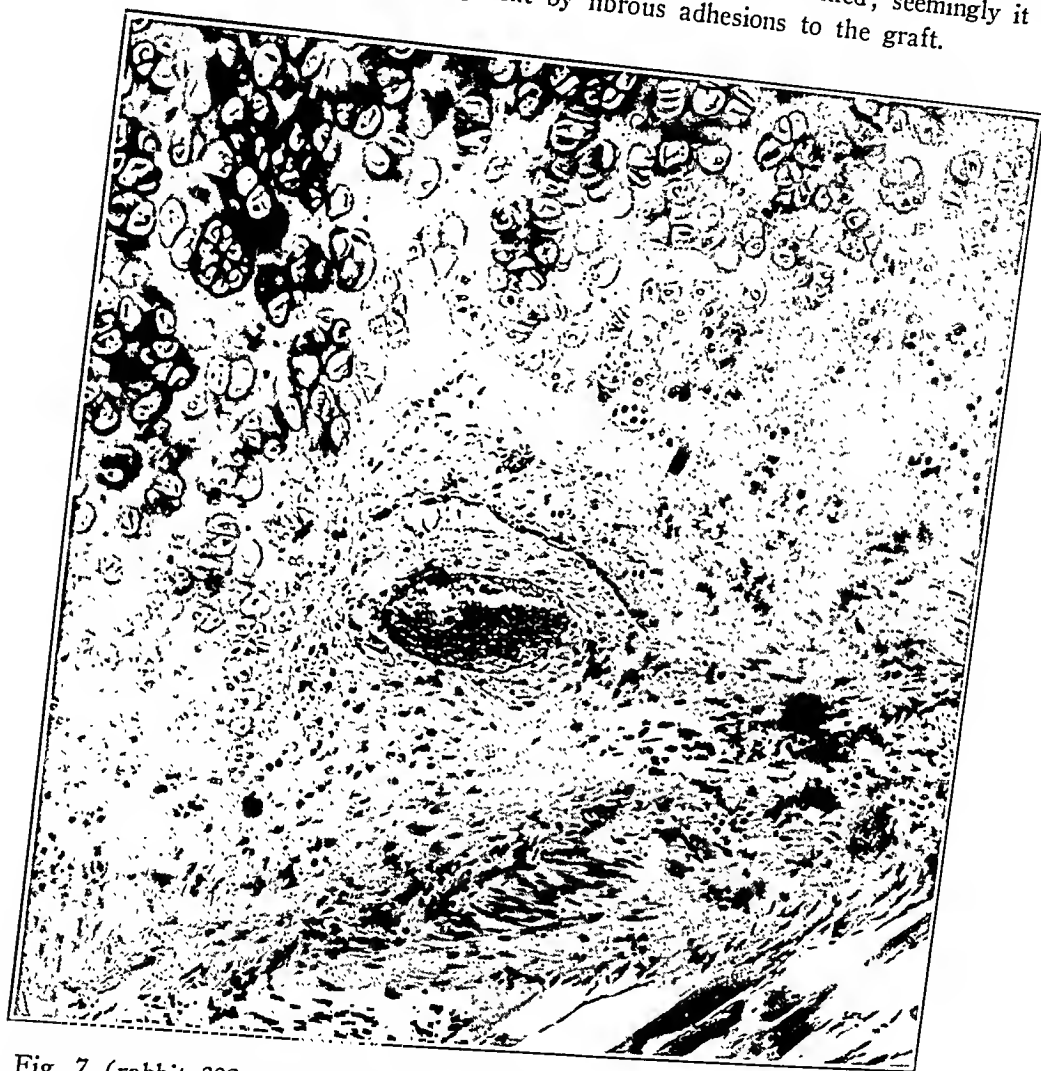


Fig. 7 (rabbit 302, series 1).—Blood vessels located in the perichondrium and partially surrounded by young proliferating cartilage cells. A few strands of striated muscle can be seen in the lower right hand corner.

Series 2: Isotransplants of Ear Cartilage in Young Rabbits.—Procedure: In this series the age of the young rabbits at the time of transplantation was 12 to 24 days (average, 20 days). By a method comparable to that used in the preceding group, 6 separate measured pieces of ear cartilage were inserted into the subcutaneous tissues of the back in litter mates. In another group, 6 implants were put beneath the skin of the back in rabbits of different breed. Likewise, 2 further portions of ear cartilage of equal size from rabbits not genetically related were exchanged and sutured into the aural defects. One infection occurred in this series.

Results: At the end of the average period of growth for this series, 173 days, each individual transplant demonstrated unmistakable gross increase in size. The control ears during this same period averaged 107 per cent increase in length, while the grafts showed but 56 per cent greater length. The surface area of these transplants indicated 155 per cent of growth, as compared with 328 per cent (calculated) for their controls. From these data it is obvious that the isografts did not grow so vigorously as did the autogenous transplants in the preceding series.

The comparison of the 6 isografts in litter mates with the group of 6 pieces inserted into similar areas on rabbits of a different breed provided an average increase of length by 52 per cent in 135 days for the litter mates and 61 per cent during a period of 198 days for the latter group. In averaging the growth in surface area, the result was 172 per cent, as compared with 156 per cent for

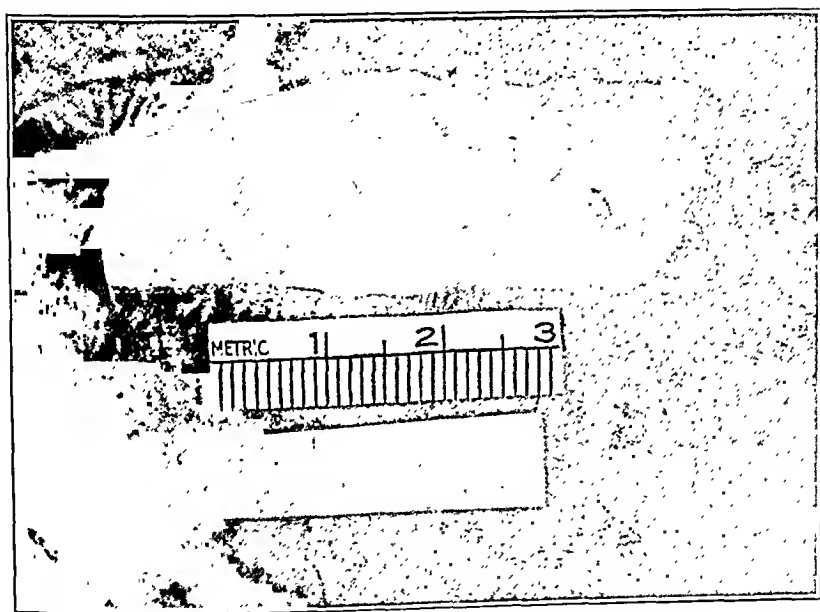


Fig. 8 (rabbit 261, series 2).—Photograph of an isograft of young ear cartilage with a piece of paper below the metric scale to show the size of the graft before transplantation. During a period of 164 days in the subcutaneous tissues of a nonrelated rabbit it increased in length 78 per cent and in area 300 per cent, which is well above the average for the entire series of isografts.

the nonrelated group. In this series, then, isografts from one breed to another averaged approximately the same increase in size as similar grafts in litter mates.

In 2 instances in which cartilage was exchanged and replaced in the ears there was slightly less growth (53 per cent increase in length and 102 per cent increase in area) than the average for the whole series, notwithstanding the fact that the grafts were undisturbed for 215 days. The transplants in this series were restricted by more fibrous adhesions, with the frequent discovery at autopsy of wrinkling and folding in the grafts. This introduced greater error in their measurement and to a considerable degree accounted for the decreased growth as compared with the autotransplants.

Microscopic Observations: So far as general appearance was concerned, the living cartilage in these sections was similar to that in the autogenous group. Again each graft had a normal basophilic matrix with living cellular elements. In this series, however, there was substantially more fibrous tissue about the transplants, although no absorption or invasion by connective tissue was discovered. Several of the sections showed a mild lymphocytic reaction about the cartilage even after 164 days; lymphocytes were not seen in the autogenous group. In contrast to the preceding group of autogenous grafts, several localized areas of necrosis were found, and staining variations in the matrix appeared more fre-

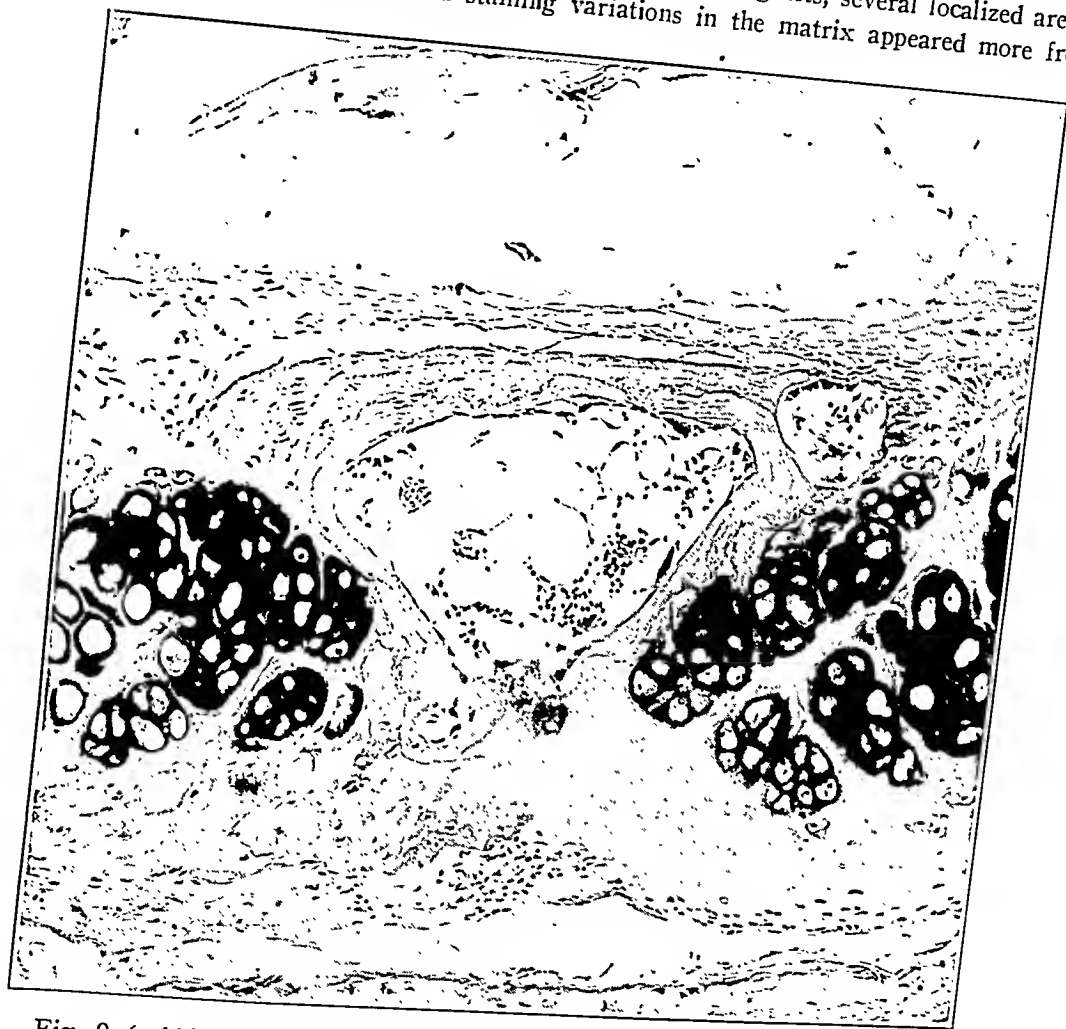


Fig. 9 (rabbit 319, series 2).—Photomicrograph showing formation of osteoid tissue in an isotransplant of young ear cartilage which had been buried in the subcutaneous tissues of a rabbit of different breed for 215 days. Degenerating cartilage cells are visible in the lower central portion, and immediately above are cellular elements of bone marrow.

quently. In sections of 4 transplants, 215 days old or more, there were unmistakable small areas of bone formation (fig. 9.) Three of these were in the cartilage while the other was adjacent to it, but there was no other calcification. Also, there were some cellular elements of bone marrow about the trabeculations of this osteoid tissue. As in the preceding series, only fibrous tissue united the graft to the bordering cartilage of the ear, with no true bridging by cartilaginous cells.

TABLE 2.—Results in Second Series

Position of Graft	Number and Breed of Rabbit	Age at Operation, Days	Duration of Experiment, Days	Weight, Gm.		Ear Length, Cm.		Per Cent Increase in Ear Length	Size of Graft, Cm.		Per Cent Increase in Length of Graft	
				Operation	Autopsy	Operation	Autopsy		Operation	Autopsy		
Subcutaneous.....	307 (White)	24	40	280	1,100	5.1	9.7	90	1.2 × 0.5	1.5 × 0.9	25	125
Subcutaneous.....	308 (White)	24	219	325	2,700	5.1	11.5	126	1.4 × 0.45	2.8 × 1.0	100	223
Subcutaneous.....	298 (Chinchilla)	16	223	230	2,235	4.1	11.0	163	2.0 × 1.35	2.2 × 1.9	10	53
Subcutaneous.....	300 (Chinchilla)	16	128	230	4.0	10.0	150	1.8 × 1.5	3.0 × 2.8	67	215
Subcutaneous.....	273 (Chinchilla)	23	94	310	1,475	5.5	11.0	100	1.15 × 0.7	1.6 × 1.15	39	139
Subcutaneous.....	263 (Chinchilla)	23	106	330	1,055	5.5	10.0	82	1.4 × 0.6	2.4 × 1.0	72	186
Subcutaneous.....	261 (Dutch)	18	164	275	1,485	4.0	8.8	120	2.8 × 0.8	5.0 × 1.8	78	300
Subcutaneous.....	262 (Chinchilla)	18	164	325	2,350	5.1	11.5	125	2.6 × 0.6	4.2 × 1.0	62	169
Subcutaneous.....	319 (White)	21	215	365	2,425	6.0	10.2	70	0.9 × 0.45	1.6 × 0.8	73	157
Subcutaneous.....	320 (Dutch)	17	215	265	1,515	4.0	8.3	107	0.8 × 0.7	1.3 × 1.1	63	155
Subcutaneous.....	319 (White)	21	215	365	2,425	6.0	10.2	70	0.8 × 0.7	1.1 × 0.9	37	76
Subcutaneous.....	320 (Dutch)	17	215	265	1,515	4.0	8.3	107	0.8 × 0.75	1.2 × 0.9	50	80
Ear.....	319 (White)	21	215	365	2,425	6.0	10.2	70	0.6 × 0.65	0.9 × 0.8	50	85
Ear.....	320 (Dutch)	17	215	265	1,515	4.0	8.3	107	0.7 × 0.5	1.1 × 0.7	57	120
General average.....	14 grafts	20	173	107	56	155
Litter mates, average.....	6 grafts	21	135	109	62	172
Nonrelated, average.....	6 grafts	19	198	100	61	166
Ear, average.....	2 grafts	19	215	88	63	102

Both grossly and microscopically many of these isografts showed a greater tendency to wrinkle and fold on themselves during growth. The constrictive action of the increased mass of fibrous tissue seen macroscopically and microscopically may afford an explanation of this observation. The gross appearance of these transplants, except for the presence of a greater number of adhesions, was identical with that of the previous living autografts.

The discrepancy between the average increase in length of the control ear in this group (107 per cent) and in the autogenous series (128 per cent) was probably the result of several factors. For the isografts the animals at operation

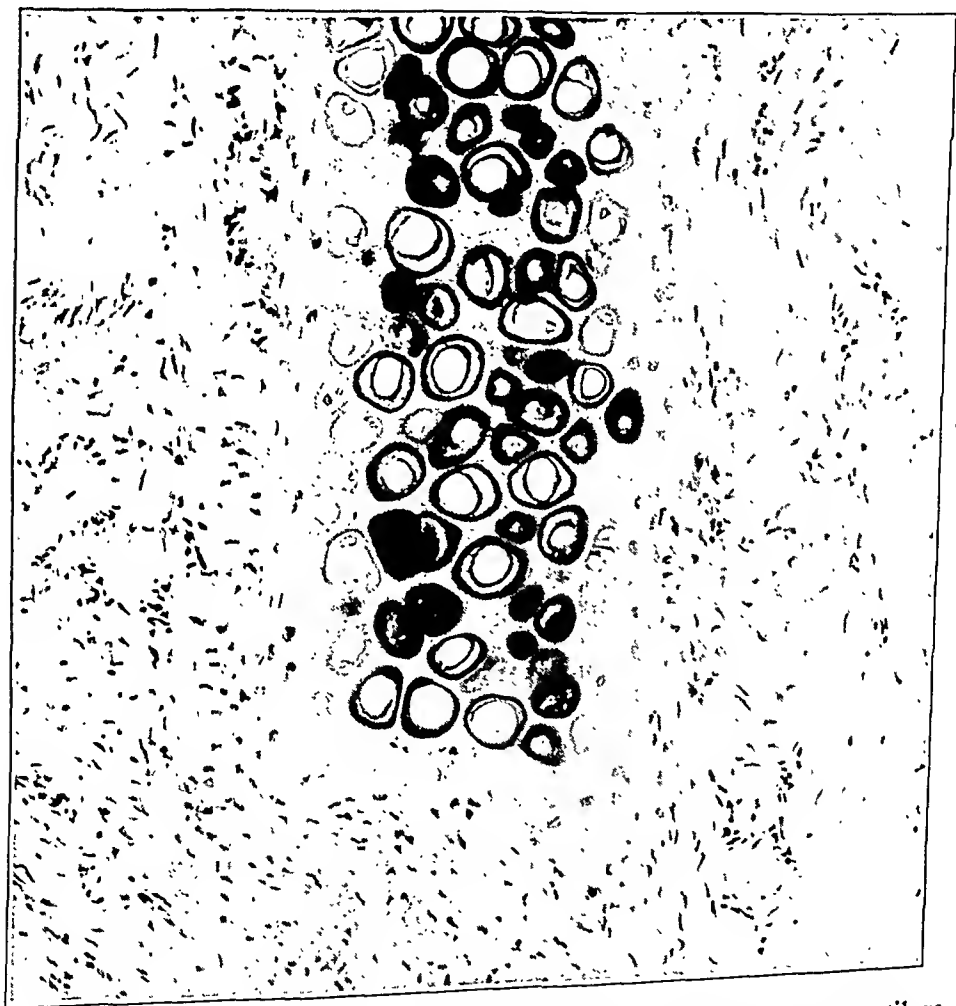


Fig. 10 (rabbit 263, series 3).—Photomicrograph of an adult ear cartilage isograft surrounded by fibrous tissue, showing a cross section of one cut edge. Despite transplantation for 106 days in the subcutaneous tissues of a young rabbit the cut end remains square and no proliferation of young cartilage cells is seen. This presents a striking contrast to the young cartilage graft of figure 6.

were, on an average, 3 days older, at a period when the ear grows rapidly, and several more rabbits of the smaller (Dutch) breed were employed. These factors, combined with a certain experimental error, may account for the apparent reduced growth in the control ears of this series.

An incidental observation of interest was found in most of the donor ears. The cartilaginous defects after removal of the grafts increased in length and area at about the same rate as did normal ears. The cut edges remained sharp, with no visible cartilaginous repair in these large spaces.

Series 3: Isotransplants of Adult Ear Cartilage into Young Rabbits.—Procedure: A small group of transplants was studied to determine the possibility of growth in adult cartilage transplanted to young animals. The rabbits employed were 18 to 24 days old. In 4 instances measured grafts of the mother's ear

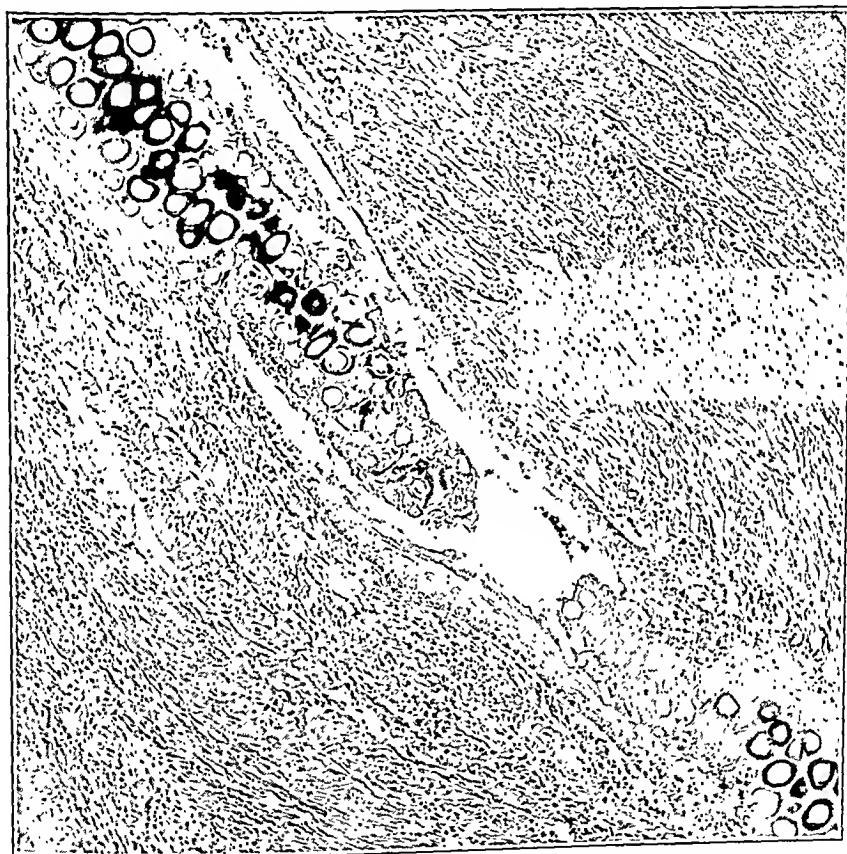


Fig. 11 (rabbit 307, series 3).—Photomicrograph of an ear cartilage graft which shows an implantation cyst separating the ends of the broken cartilage plate. Epithelial cells have advanced along the border of the cartilage.

cartilage were sutured into openings in the cartilage (of the same size and shape) in the ears of the young rabbit. Using the subcutaneous tissues of the back in the same animals, 4 similar portions of the mother's ear cartilage were inserted. For comparison, 2 pieces of ear cartilage from an adult rabbit not related to the young hosts (and of different breed in 1 case) were placed beneath the skin of the back in these young animals. Finally, as a corollary, 2 sections of young ear cartilage were inserted subcutaneously into an adult animal of a different strain. The wounds healed well, and no infections occurred.

TABLE 3.—Results in Third Series

Position of Graft	Number and Breed of Rabbit	Origin of Graft	Age at Operation, Days	Duration of Experiment, Days	Weight, Gm.		Ear Length, Cm.		Per Cent Increase in Ear Length	Size of Graft, Cm.		Per Cent Increase in Length of Graft
					Operation	Autopsy	Operation	Autopsy		Operation	Autopsy	
Ear.....	307 (White)	Mother's ear	24	40	280	1,100	5.1	9.7	90	1.4 × 0.15	1.4 × 0.4	No change
Subcutaneous.....	307 (White)	Mother's ear	24	40	280	1,100	5.1	9.7	90	1.5 × 0.9	1.45 × 0.95	No change
Ear.....	308 (White)	Mother's ear	24	219	325	2,700	5.1	11.5	126	1.2 × 0.5	1.2 × 0.5	No change
Subcutaneous.....	308 (White)	Mother's ear	24	219	325	2,700	5.1	11.5	126	1.45 × 0.95	1.5 × 0.9	No change
Ear.....	273 (Chinehilla)	Mother's ear	23	94	310	1,475	5.5	11.0	100	1.4 × 0.6	1.5 × 0.4	3
Subcutaneous.....	273 (Chinehilla)	Mother's ear	23	94	310	1,475	5.5	11.0	100	1.5 × 1.05	1.5 × 1.1	7
Ear.....	203 (Chinehilla)	Mother's ear	23	106	330	1,655	5.5	10.0	82	1.15 × 0.7	0.9 × 0.4	No change
Subcutaneous.....	203 (Chinehilla)	Mother's ear	23	106	330	1,655	5.5	10.0	82	1.4 × 1.15	1.4 × 1.15	Decrease
Subcutaneous.....	201 (Dutch)	Adult white	18	164	...	1,485	4.0	8.8	120	2.5 × 1.3	2.5 × 1.3	No change
Subcutaneous.....	262 (Chinehilla)	Adult white	18	164	...	2,350	5.0	11.5	130	2.1 × 1.3	1.7 × 1.2	No change
Subcutaneous.....	317 (Dutch)	21 day old	210	55	1.3 × 0.8	2.4 × 1.4	Decrease
Subcutaneous.....	317 (Dutch)	chnehillia	210	55	0.9 × 0.9	1.5 × 1.1	85
Subcutaneous.....	318 (White)	21 day old	210	55	1.35 × 1.1	Lost inf.	66
Subcutaneous.....	318 (White)	21 day old	210	55	0.9 × 0.9	2.1 × 1.7	..
Subcutaneous.....	10 grafts	chnehillia	210	55	105	133
Adult, average.....	1 grafts	210	55	No change
Young, average.....	1 grafts	210	55	95

Results: After an average period of 125 days, the 10 specimens of adult cartilage exhibited no measurable increase in size. At the same time only 2 grafts had diminished definitely in size from gross absorption. Some of these pieces were softer than the previously observed young cartilage grafts, and several had assumed a brownish color suggestive of reduced vitality. All were surrounded by adherent scar tissue, and there were some wrinkling and folding of the edges. The 4 transplants placed in ear defects had maintained their original size only, while the adjacent young cartilage in its efforts to expand was constricted into folds and corrugations along the borders of the graft.

In direct contrast, we found excellent growth in the young transplants buried in adult rabbits of a different breed. In 55 days there was a 95 per cent increase in length and a 223 per cent increase in area. As had been anticipated, demonstrable growth in a transplant depends primarily on the age of the cartilage and not on the age of the host tissues.

Microscopic Observations: Each section of adult cartilage contained well stained matrix, fewer but well preserved cells and a thinner intact perichondrium. There were several localized areas of degeneration, and in 1 section apparent absorption with replacement by fibrous tissue had taken place. On the whole, this adult cartilage was well preserved but showed practically no growth activity at the cut edges. In contrast to the cartilage in young grafts, its sharp, square edges were not covered with proliferating perichondrium, although an abundance of fibrous tissue was present around the grafts (fig. 10).

Two implantation cysts were discovered (fig. 11) and one area of localized osteoid tissue was observed, but again there was no calcification of cartilage. In 2 grafts of adult cartilage placed into window-like defects of the young ear an actual bridging of the gap by new cartilage cells was seen for the first time. The greater portion of this proliferation seemed to arise from the adjacent young cartilage. Henle⁴⁸ (1907), while transplanting cartilage from rabbits' ears, had observed this same type of bridging by young cartilage cells. In the 2 adult grafts in which there was gross absorption, the remaining cartilage was living but surrounded by an increased amount of connective tissue. One area of apparent metaplasia of fibrous tissue into cartilage was discovered in this section.

The microscopic appearance of the young cartilage grafts in this series was not unusual except for a considerable lymphocytic infiltration in 1. In the other there was so much constriction from the dense fibrous tissue capsule about the graft that the cartilage had folded back on itself in its effort to expand.

Series 4: Autotransplants and Isotransplants of Rib Cartilage into Young Rabbits.—Procedure: In rabbits 12 to 18 days old, 4 measured portions of costal cartilage were transplanted to the subcutaneous tissues of the abdomen as autografts. Two pieces of rib cartilage were dissected free and then returned to the donor area, and 2 further pieces were implanted beneath the skin of the abdomen as isografts in nonrelated rabbits. Also, a mass of perichondrium scraped from a costal cartilage was buried beneath the skin.

Results: After a period of 133 days (average), 3 of the 4 autotransplants increased in length by 30 per cent. The remaining graft had been broken into two irregular pieces, with indication of slight absorption about the rounded ends. In the case of autografts left in place in the thoracic cage definite identification of the resected piece was impossible, for depressed irregular reconstruction with cartilaginous union had occurred. The 4 isografts showed but 22 per cent increase

48. Henle, A.: Zur Technik der Nasenplastik, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 1887, 3, 161.

TABLE 4—*Re.*

TABLE 4— <i>Re.</i>											
Position of Graft	Number and Breed of Rabbit	Age at Operation, Days	Duration of Experiment, Days	<i>Series</i>				Per Cent Increase in Weight	Size of Graft, Cm.		Per Cent Increase in Length
				Autotransplants	Weight, Gm.		Operation		Autopsy		
					Operation	Autopsy					
Subcutaneous.....	309 (Chinchilla)	18	217	310	2,760	694	0.5 × 0.15	1.10 × 0.2	23		
Subcutaneous.....	310 (Chinchilla)	18	49	320	1,170	265	0.85 × 0.2	broken	..		
Subcutaneous.....	309 (Chinchilla)	18	217	310	2,760	694	0.75 × 0.2	1.05 × 0.2	10		
Donor site.....	315 (White)	18	49	330	1,170	265	0.75 × 0.15	0.85 × 0.1	13		
Donor site.....	315 (White)	16	49	285	800	181	0.9 × 0.2	?	..		
Donor site.....	316 (White)	16	210	270	2,720	901	1.25 × 0.2	?	..		
Donor site.....	316 (White)	16	210	270	2,720	901	1.2 × 0.2	?	..		
Subcutaneous.....	313 (Dutch)	12	208	360	1,605	316	1.4 × 0.25	1.7 × 0.25	21		
Subcutaneous.....	314 (White)	16	208	530	2,745	418	1.2 × 0.18	1.4 × 0.2	17		
Subcutaneous.....	313 (Dutch)	12	208	360	1,605	316	1.4 × 0.2	1.8 × 0.25	29		
Subcutaneous.....	314 (White)	16	208	530	2,745	418	1.05 × 0.18	1.3 × 0.2	..		
General average.....	4 autografts	17	133	479		
General average.....	4 isografts	14	208		

TABLE 5.—*Results in Fifth Series*

Fifth Series									
Position of Graft	Number and Breed of Rabbit	Method of Fixing	Age at Operation, Days	Duration of Experiment, Days	Weight, Gm.		Size of Graft, Cm.		Result
					Autotransplants (Ear Cartilage)	Autopsy	Operation	Autopsy	
Subcutaneous	315 (White)	Alcohol	16	55	285	800			
Subcutaneous	315 (White)	Merthiolate	16	55	285	800			
Subcutaneous	315 (White)	Freezing	16	55	285	800			
Subcutaneous	316 (White)	Alcohol	16	216	270	2,720			
Subcutaneous	316 (White)	Merthiolate	16	216	270	2,720			
Subcutaneous	316 (White)	Freezing	16	216	270	2,720			
Subcutaneous	313 (Dutch)	Alcohol	12	216	223	1,605			
Subcutaneous	313 (Dutch)	Merthiolate	12	216	223	1,605			
Subcutaneous	313 (Dutch)	Freezing	12	216	223	1,605			
Subcutaneous	314 (White)	Alcohol	16	216	280	2,745			
Subcutaneous	314 (White)	Merthiolate	16	216	280	2,745			
Subcutaneous	314 (White)	Freezing	16	216	280	2,745			
Subcutaneous	317 (Dutch)	Alcohol	24	243	325	1,500			
Subcutaneous	317 (Dutch)	Merthiolate	24	243	325	1,500			
Subcutaneous	317 (Dutch)	Freezing	24	243	325	1,500			
Subcutaneous	318 (White)	Alcohol	28	243	385	2,160			
Subcutaneous	318 (White)	Merthiolate	28	243	385	2,160			
Subcutaneous	318 (White)	Freezing	28	243	385	2,160			

in length in 208 days, but this difference is less striking than that observed in ear cartilage grafts.

Microscopic Observation: There was no essential difference in the microscopic picture of autografts and isografts, for in all cases the cartilage appeared normal and living. The sharp cut ends of each graft had been rounded as the perichondrium had grown over the edge and proliferation had followed. There was an area of bone formation within the cartilage of 1 graft, but in none was there further calcification. Also, in 3 instances there was union of two portions of chondral tissue by new young cartilage. The mass of perichondrium which had been implanted for 49 days produced two distinct areas of young cartilage surrounded by normal perichondrium. Active proliferation of young cartilage tissue was observed in these regions.

On the whole, these observations for hyaline rib cartilage substantiate those for elastic ear cartilage.

Series 5: Autotransplants and Isotransplants of Preserved Ear Cartilage in Young Rabbits.—**Procedure:** The three methods employed to fix or preserve the grafts for twelve day periods were as follows: (a) 95 per cent alcohol; (b) a solution of one part aqueous mercuriolate to four parts physiologic solution of sodium chloride (O'Connor) and (c) refrigeration of the graft for five days in a moist saline sponge followed by rapid freezing and dehydration by a method similar to the procedure for quick freezing of foods.

Six measured ear cartilage autografts, 6 similar isografts from nonrelated rabbits and 6 portions of costal cartilage were treated by the aforementioned three methods, a pair of grafts being used for each. After twelve days they were transplanted into subcutaneous tissues. One section of rib cartilage, preserved by freezing, was extruded from an infected wound.

Results: After an average period of 232 days, every graft showed gross reduction in size with varying amounts of absorption. In some cases cartilage could not be found, and in others the remaining bits could not be measured accurately, which indicated that all three methods gave equally unsatisfactory results.

Microscopic Observations: All sections had dead, degenerating cartilage with no areas of living cells or regeneration. In most instances there were only fragments of pale, ghostlike cartilage structure, and fibrous tissue actively invaded these portions. Several areas of calcification were present (fig. 13), and early osteoid tissue was discovered in one region (fig. 12). The cellular structure showed granular cytoplasm with acidophilic, faded nuclei and karyolysis. There was one notable difference between these two types of grafts: Whereas the preserved ear cartilage was actively invaded and absorbed, the costal cartilage, although dead, resisted fragmentation and degeneration rather well during a period of 243 days. This may indicate that preserved hyaline cartilage withstands active absorption for longer periods than does elastic cartilage. However, the difference in physical shape and mass in these two types of transplants as they are exposed to the action of the host tissues probably plays an important role in rapidity of destruction.

Series 6: Isotransplants and Heterotransplants of Preserved Rib Cartilage into Adult Rabbits.—**Procedure:** Twelve portions of rib cartilage from adult rabbits and 12 similar pieces from adult dogs were implanted in the subcutaneous tissues of rabbits of a different breed. Four sections from each animal were buried in rabbits as fresh grafts used for controls, and the remaining portions, after equal division, were fixed for five days by each of the three methods used in series 5.

Specimens were removed for histologic examination at 7, 14 and 21 day intervals, and the final group was recovered at the time of autopsy.

Object: As Loeb³⁸ has claimed there is more toxic effect on the part of tissues toward heterotransplants than toward isotransplants, this series was included to observe the effect of different methods in fixation of cartilage grafts on the early host tissue reaction. It was considered possible that fixation might diminish those characteristics of heteroplastic cartilage which invite increased injurious action on the part of the host tissues.

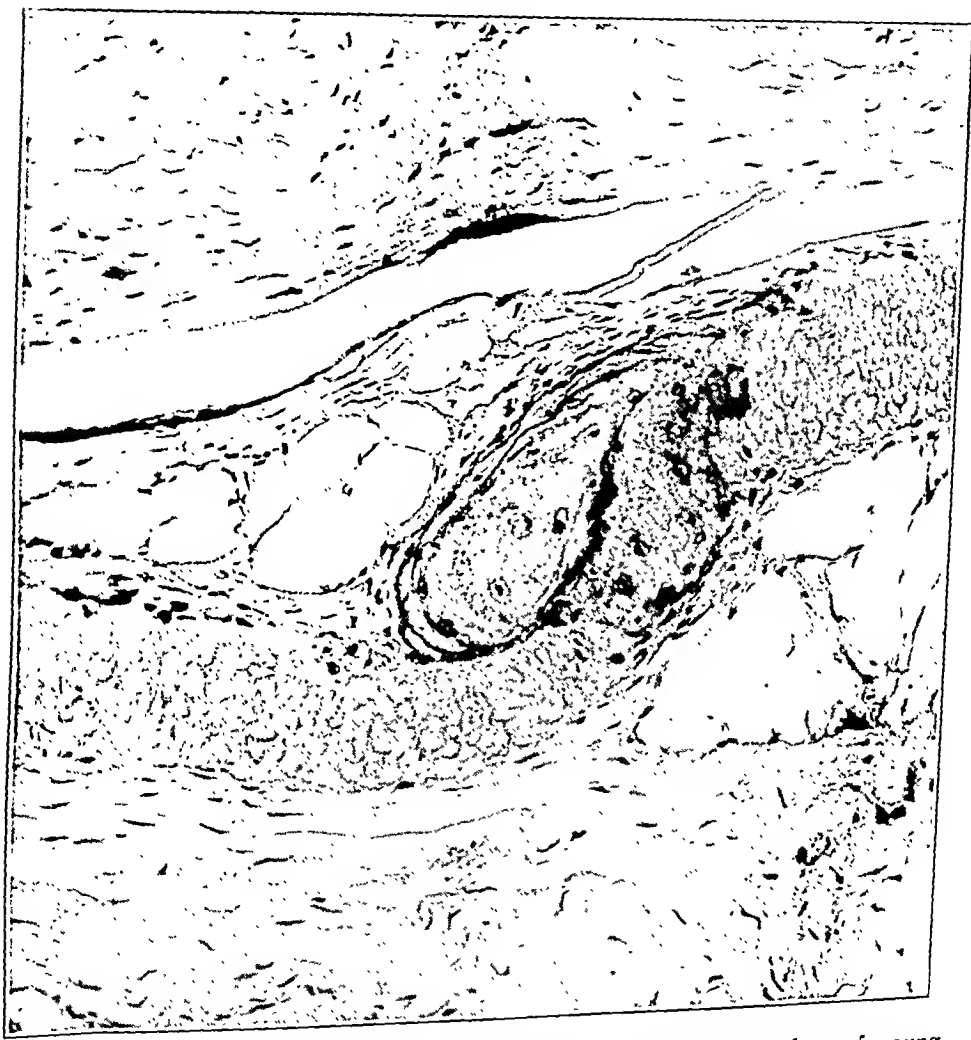


Fig. 12 (rabbit 313, series 5).—Photomicrograph of an isotransplant of young ear cartilage preserved in alcohol before implantation into the subcutaneous tissues of a young rabbit for 216 days. The dead shadow-like cartilage structure includes a localized area of osteoid tissue near the center.

Microscopic Observations: Unfortunately the 21 day sections were ruined during preparation; so the height of the lymphocytic reaction (Loeb³⁸) could not be studied.

From an estimation of the marked lymphocytic reaction in the sections of 7 and 14 days, preserved heterografts still produce a more intense reaction in sur-



Fig. 13 (rabbit 317, series 5).—Photomicrograph of a cross section of young rib cartilage, preserved by the freezing method, which had been transplanted into a growing rabbit for 243 days. Calcification is apparent in a large portion of the graft, with superficial fragmentation of the periphery.

TABLE 6.—Results in Sixth Series

Position of Graft	Number and Breed of Rabbit	Method of Fixing	Estimation of Lymphocytic Reaction			
			7 Days	14 Days	21 Days	Autopsy
Isografts of Rib Cartilage from Adult Chinchilla						
Subcutaneous	298 (Chinchilla)	Fresh	++	++++	Sections poorly fixed	+ (114 days)
Subcutaneous	273 (Chinchilla)	Alcohol	+++	++	Sections poorly fixed	Died 23 days
Subcutaneous	263 (Chinchilla)	Merthiolate	++	+	Sections poorly fixed	+ (34 days)
Subcutaneous	263 (Chinchilla)	Freezing	++++	++	Sections poorly fixed	++ (34 days)
Heterografts of Rib Cartilage from Adult Dog						
Subcutaneous	298 (Chinchilla)	Fresh	+++++	++++	Sections poorly fixed	++ (114 days)
Subcutaneous	300 (Chinchilla)	Alcohol	+++++	++++	Sections poorly fixed	++ (50 days)
Subcutaneous	273 (Chinchilla)	Merthiolate	++++	++++	Sections poorly fixed	Died 23 days
Subcutaneous	300 (Chinchilla)	Freezing	++++	+++++	Sections poorly fixed	++ (50 days)

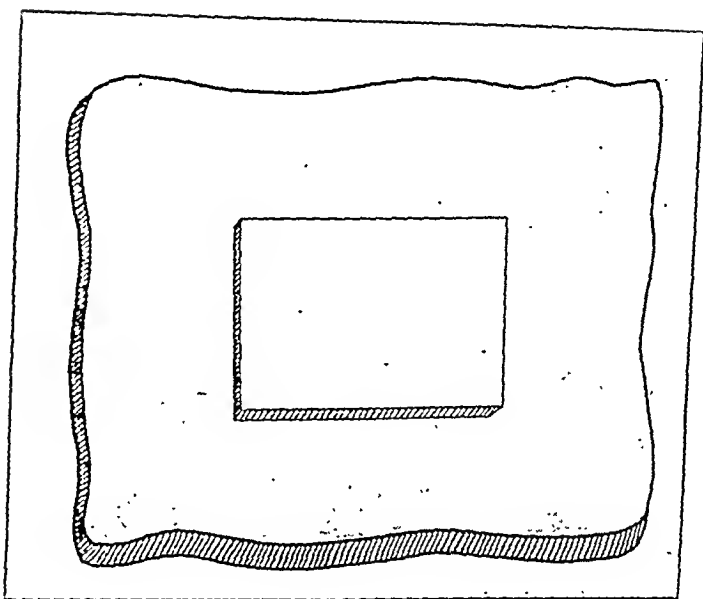


Fig. 14.—Illustration, drawn to scale, showing the average increases of 122 per cent in length and 413 per cent in area of the young ear cartilage autografts in series 1 during a period of 140 days.

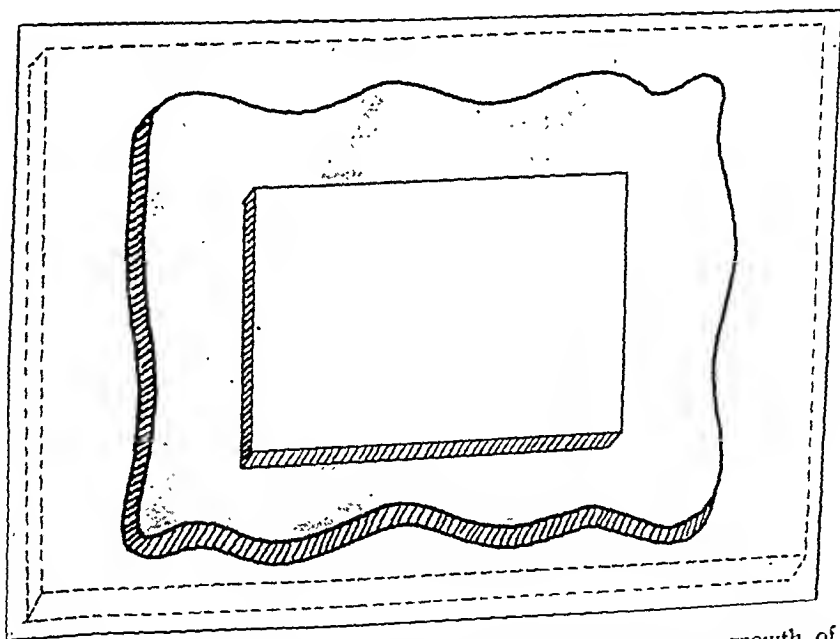


Fig. 15.—Illustration, drawn to scale, representing the average growth of the isotransplants of young ear cartilage in series 2. The original size of the graft is shown in the center, and the outer rectangle of broken lines indicates the calculated or expected growth. The grafts averaged an increase of 56 per cent in length and 155 per cent in area.

rounding tissues than do fixed isografts of cartilage. After 114 days the portion of fresh rabbit control was living and not fragmented by fibrous tissue. The corresponding control of fresh dog cartilage after the same period showed cystic degeneration, with no viable cartilage cells.

CLINICAL APPLICATION OF YOUNG CARTILAGE TRANSPLANTS

In reconstructive surgery fresh human cartilage grafts have been used successfully for many years, but these transplants have consisted mainly of adult cartilage, in which the growth factor is excluded. Recently the importance of correcting certain acquired or congenital deformities during childhood in order to avoid any unfortunate psychopathic sequelae has been recognized. For children whose disfigurement is a marked depression of the nasal bridge, the simplest corrective procedure would employ preserved cartilage. A more satisfactory result might be assured with a fresh transplant of rib cartilage from one parent, but either procedure would probably necessitate the insertion of a larger graft when the child was grown. Therefore, despite the increased operative procedure involved in securing autogenous rib cartilage, the prospect of a permanent transplant which would increase in size with the growth of the nose is an important consideration. When the problem is the reconstruction of a congenitally malformed ear, fresh autogenous cartilage as a graft which would keep pace with the growth of the normal ear would be advantageous.

During the cycle of growth the increase in size of the nose is proportionately greater than that of the ear. The estimated size of a rib cartilage graft, therefore, might require a slight overcorrection for the nose, since costal cartilage grows relatively slowly. When a mother sacrifices a portion of her ear for her child, this adult cartilaginous framework, despite its new location in young growing tissues, will never increase in size. Hence, in such cases an even greater overcorrection is required for the two ears to match when the child is grown. For cartilage grafts in children, therefore, the factor of growth in fresh autotransplants merits emphasis and consideration.

SUMMARY

A careful review of the important literature on cartilage transplantation is presented, with divisions into (a) experimental studies on fresh cartilage grafts in animals and (b) experiments with preserved cartilage.

No reported experiments on actual growth in grafts of permanent nonembryonal cartilage were discovered in the literature.

A detailed description of the technic employed in transplanting 107 separate cartilage grafts into rabbits is given.

The autografts of young ear cartilage in series 1 averaged an increase in length of 122 per cent over a period of 161 days. In all cases growth was substantiated by microscopic observations of living cartilage and by active proliferation of new cartilage cells at the cut edges of the graft.

Autogenous cartilage transplants in muscle increased in size more rapidly than did those buried beneath the skin.

Isografts of young ear cartilage increased in length by 56 per cent over a period of 173 days (average). Isotransplantation between litter mates as compared with rabbits of different breed produced approximately the same percentage of growth. Also, unmistakable proof of viability and proliferation of new cartilage cells was present in all microscopic sections, and in this group four separate areas of osteoid tissue were discovered.

In no instance was any measurable increase in size observed after an average period of 125 days in adult isografts placed in young rabbits. In contrast, young cartilage grafts in adult host tissue grew exceedingly well.

Less rapid increase in length was observed in autotransplants and isotransplants of young rib cartilage, but in every way macroscopic and microscopic observations substantiated the preceding statements on growth in ear grafts.

Before implantation, eighteen transplants of young rib and ear cartilage were preserved for twelve day periods by three different methods. Varying amounts of macroscopic reduction in size occurred in every instance, and all sections demonstrated dead degenerated cartilage structure with some areas of calcification. Microscopically, the rib cartilage transplants resisted absorption much better than did the thin ear grafts.

At 7 and 14 day intervals, heterografts of preserved dog costal cartilage produced a more intense lymphocytic reaction on the part of the host tissues than did isografts of fixed rabbit cartilage.

CONCLUSIONS

1. Both autotransplants and isotransplants of young rabbit cartilage will grow.
2. Isografts of adult ear cartilage do not increase in size even when placed in the tissues of very young rabbits.

3. Cartilage growth depends on intrinsic factors and is not influenced by the age of the surrounding tissues of the host.

4. Transplants of cartilage grow more vigorously in tissues with greater vascularity.

5. If the aforementioned results can be obtained with other experimental animals, they should have a limited but definite clinical application in plastic and reconstructive procedures on children.

Dr. Jerome P. Webster stimulated my interest in this problem and made helpful suggestions. Drs. A. P. Stout and Robert Hill interpreted the microscopic slides.

CAPILLARY PERMEABILITY AND INFLAMMATION IN RABBITS GIVEN HEPARIN

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Observations on the mechanism of capillary permeability and its relation to inflammation have been the basis for a series of papers by one of us. In these it has been shown that the phenomenon considered to be an increase in capillary permeability as indicated by the localization and concentration of trypan blue following an intravenous injection represents a change which apparently occurs in the epithelial cells, connective tissue cells and endothelial cells after either injection or application of any one of many different types of irritants.¹ This increase in permeability represents a temporary change in the cells, as shown by the localization and concentration of trypan blue in the skin of the rabbit for only three hours after the local application of xylene. The greatest quantity of trypan blue localizes in the area where xylene is applied the shortest time before the dye is given.²

The time in which trypan blue after an intravenous injection localizes and concentrates in areas of inflammation is not determined by either the presence or the absence of edema and hyperemia. Furthermore, the time in which polymorphonuclear leukocytes appear in the extravascular tissues in areas of inflammation is different from the time in which trypan blue localizes in its greatest quantity in the skin of the rabbit.³ It is evident from these observations that capillary permeability as shown by the localization and concentration of trypan blue is a phenomenon different from that which permits the localization of polymorphonuclear leukocytes in areas of inflammation.

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From the Department of Pathology and the Department of Surgery, the University of Tennessee.

1. Rigdon, R. H.: Relation of Capillary Permeability to Inflammation, *South. M. J.* **34**:292, 1941.

2. Rigdon, R. H.: (a) Capillary Permeability in the Skin of the Rabbit, *Proc. Soc. Exper. Biol. & Med.* **42**:43-45, 1939; (b) Capillary Permeability in Areas of Inflammation Produced by Xylene, *Arch. Surg.* **41**:101 (July) 1940.

3. Rigdon (footnotes 1 and 2 b).

Capillary permeability and inflammation have been studied in narcotized rabbits.⁴ Pickrell^{4a} in 1938 showed that leukocytes failed to localize about pneumococci in the skin of rabbits intoxicated with ethyl alcohol. Cressman and one of us (R. H. R.)^{4b} confirmed these observations. None of these investigators, however, were able satisfactorily to explain this phenomenon. One of us (R. H. R.)⁵ has recently shown that epinephrine influences capillary permeability and the localization of leukocytes about foci of bacteria in the skin of the rabbit. It has been suggested that vascular constriction may explain these observations when epinephrine is used.

The mechanism of vascular changes and of chemotaxis has been studied frequently since the observations of Cohnheim and Metchnikoff. Leukocytes have been described as "sticking" to the endothelial cells in the small blood vessels in areas of inflammation.⁶ Present knowledge is meager as regards the changes in the endothelial cells and the mechanism by which leukocytes concentrate in areas of inflammation. Since heparin is an anticoagulant, it was thought that the presence of this substance in large quantities in the blood of the rabbit might influence capillary permeability and the localization of leukocytes in areas of inflammation. This paper is a report of our studies on the effects of heparin⁷ on capillary permeability and inflammation in the rabbit.

EFFECT OF HEPARIN ON CAPILLARY PERMEABILITY

Capillary permeability in the normal rabbit may be studied by carefully applying xylene with a cotton applicator to local areas of skin at frequent intervals, after which 10 cc. of a 0.2 per cent solution of trypan blue is given intravenously. This dye localizes first and in greatest quantity in the area of skin where xylene is applied the shortest time before the dye is given. When the interval between the application of xylene and the injection of the dye is three hours or longer, no more dye localizes and concentrates in the xylene-treated areas than in the untreated skin.^{2b}

In the present experiment 4 rabbits were used. The skin was carefully shaved twenty-four hours or longer before the xylene was applied. Each animal was given intravenously 4,000 units of heparin. The

4. (a) Pickrell, K. L.: The Effect of Alcohol Intoxication and Ether Anaesthesia on Resistance to Pneumococcal Infection, *Bull. Johns Hopkins Hosp.* **63**: 238, 1938. (b) Cressman, R. D., and Rigdon, R. H.: Permeability and Inflammation in Narcotized Rabbits, *Arch. Surg.* **39**:586 (Oct.) 1939.

5. Rigdon, R. H.: A Study of Capillary Permeability and Inflammation in the Skin of Rabbits Given Adrenalin, *Surgery* **8**:839, 1940.

6. Clark, E. R., and Clark, E. L.: Observations on Changes in Blood Vascular Endothelium in the Living Animal, *Am. J. Anat.* **57**:385, 1935.

7. The heparin used in these experiments was supplied to us by Roche-Organon

heparin was diluted with equal parts of physiologic solution of sodium chloride. This quantity of heparin prevented the clotting of blood, as is shown by the data:

Rabbit	Quantity of Heparin, Units	Clotting Time, Minutes
560	4,000	50+
561	4,000	45+
562	4,000	35+
563	4,000	25+
A	0	5
B	0	3
C	0.	5
D	0	4

(To determine the clotting time of blood, 10 cc. is taken from the heart and 2 cc. is put into each of three test tubes [1 by 10 cm.]. The tubes are inverted each minute during the first twenty minutes and thereafter at five minute intervals. Clotting is complete when the tubes can be inverted without escape of the blood.)

Xylene was applied to the skin three hours, two hours, one hour, thirty minutes and immediately before 10 cc. of a 0.2 per cent solution of trypan blue was injected intravenously. Heparin (4,000 units) was injected intravenously thirty minutes before the injection of the dye. Trypan blue localized and concentrated within five minutes in the last area where xylene had been applied. The dye subsequently localized and concentrated in the other xylene-treated areas of skin. There was a progressive diminution in the quantity of dye in the skin when the interval between the application of the xylene and the injection of the dye was increased. There was no difference either in the time or in the quantity of dye that localized in the xylene-treated areas of skin in rabbits given heparin and in the controls.

EFFECT OF HEPARIN ON THE LOCALIZATION OF STAPHYLOCOCCI IN AREAS OF INFLAMMATION

Staphylococci in suspension in saline solution when given intravenously to rabbits localize and concentrate in xylene-treated areas of skin in a manner similar to the localization of trypan blue.⁸ The skin of 6 rabbits was prepared for use in the present experiment. Four of these animals were given intravenous injections of 2,000 units of heparin. The injections were made at forty-five minute intervals. Fifteen minutes after the second injection of heparin, xylene was applied to a local area of the skin and 10 cc. of a saline suspension of staphylococci was injected intravenously. The rabbits were killed one hour after injection of the bacteria. The xylene-treated area of skin was removed from

8. Rigdon, R. H.: Localization of Staphylococci in Areas of Inflammation Produced by Xylene, *Arch. Surg.* 41:879 (Oct.) 1940.

each of the 6 animals. The sections of skin were divided, and one part was fixed immediately in a 10 per cent concentration of solution of formaldehyde U. S. P. The second part was put into the incubator at 37.5 C. The tissue was removed after five hours and placed in the solution of formaldehyde. Paraffin sections were prepared and were stained with hematoxylin and eosin.

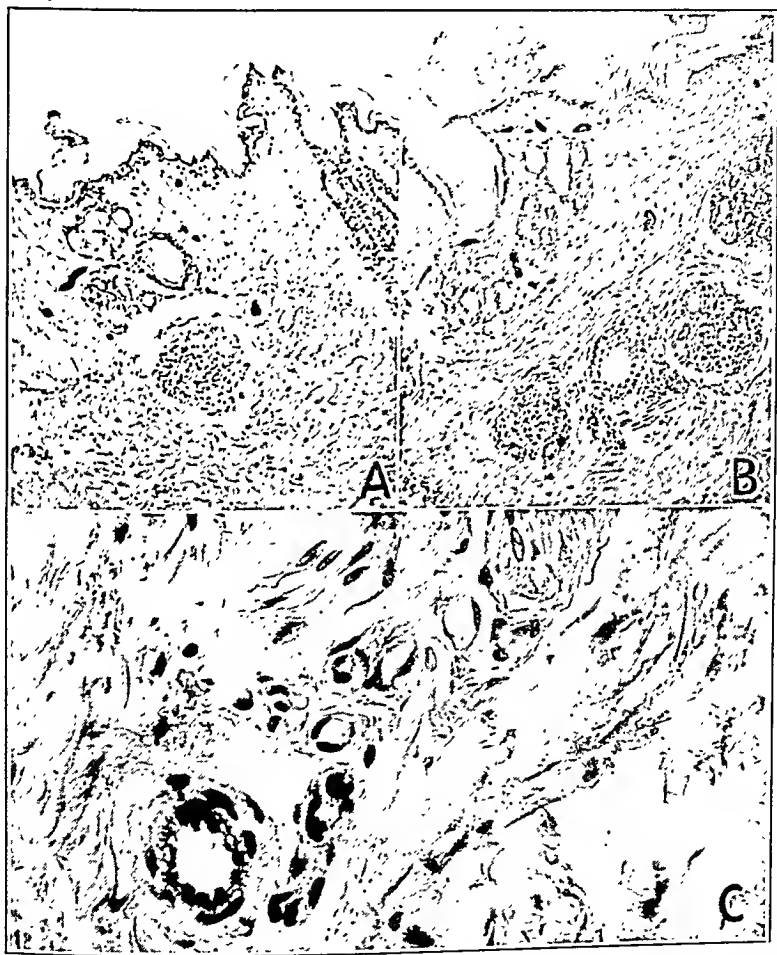


Fig. 1.—Staphylococci after an intravenous injection localize in the small blood vessels immediately below the squamous epithelium in the area where xylene has been applied. *A*, heparin (2,000 units) was given to a rabbit fifteen minutes before the xylene was applied. A saline suspension of staphylococci was given immediately after application of the xylene. *B*, control for *A*. Apparently there is no difference in *A* and *B*. *C*, portion of the same section shown in *B*. Note the absence of bacteria in the lumen of the small vessels in the subcutaneous tissues.

The staphylococci multiply in the lumens of the small blood vessels during incubation, as shown in figure 1. Apparently heparin has no

effect on the localization and concentration of staphylococci in areas of inflammation. Figure 1 *A* shows the accumulation of staphylococci in the small vessels in the corium. Figure 1 *B* shows the reaction in the control. The lumen of every blood vessel in this portion of the skin was not filled. However, we could see no difference in the number of the vessels involved in the experimental and in the control group. (When xylene is applied to the skin and staphylococci are given intravenously, the bacteria localize only in the small vessels immediately beneath the squamous epithelium. Figure 1 *C* is a portion of the section shown in figure 1 *B*. There were several small vessels here, but staphylococci were not present in any of them.)

EFFECT OF HEPARIN ON THE LOCALIZATION OF LEUKOCYTES IN AREAS OF INFLAMMATION

It is evident from the two preceding experiments that heparin when given intravenously does not influence the localization and the concentration of either trypan blue or staphylococci in xylene-treated areas of skin in the rabbit. To study the effect of heparin on the localization of polymorphonuclear leukocytes in areas of inflammation, 9 rabbits were used. Six of these were given intravenously 2,000 units of heparin. This quantity of heparin was injected a second time forty-five minutes later and again forty-five minutes later. Immediately after the first injection of heparin, 0.2 cc. of a heavy saline suspension of staphylococci was injected subdermally into two areas on the side of the abdomen. Three rabbits were used for the controls. All of the rabbits were killed two hours after the injection of the staphylococci. Sections of the skin from the areas into which the organisms had been injected were removed and fixed in a 10 per cent concentration of solution of formaldehyde U. S. P. Histologic preparations were made and stained with hematoxylin and eosin.

There appeared to be less macroscopic inflammation in some of the rabbits given heparin than was present in some of the controls. Microscopic studies showed some variation in the number of leukocytes about the bacteria in both the normal and the heparinized animals. The variation in the number of leukocytes, however, in the two groups was considered insignificant.

It was thought that should heparin have any influence on the localization of leukocytes in areas of inflammation it might become evident if the aforescribed experiment were carried on for four hours instead of for only two hours. Each of 4 rabbits, therefore, was given intravenously 2,000 units of heparin every forty-five minutes for six injections. Two-tenths cubic centimeter of a heavy saline suspension of staphylococci was injected subdermally immediately after the first injection of heparin. The injection of staphylococci was repeated two hours later. Two rabbits were used for controls. The animals were

killed four and one-half hours after the first injection of heparin. The skin at the site of the bacterial inoculation was removed and fixed in solution of formaldehyde. Histologic preparations were made and stained with hematoxylin and eosin.

There was no apparent difference in the number of leukocytes around the staphylococci in the heparinized rabbits as compared with the controls (fig. 2). A large number of red blood cells were present in the inflammatory area in some of the rabbits to which heparin had been given.

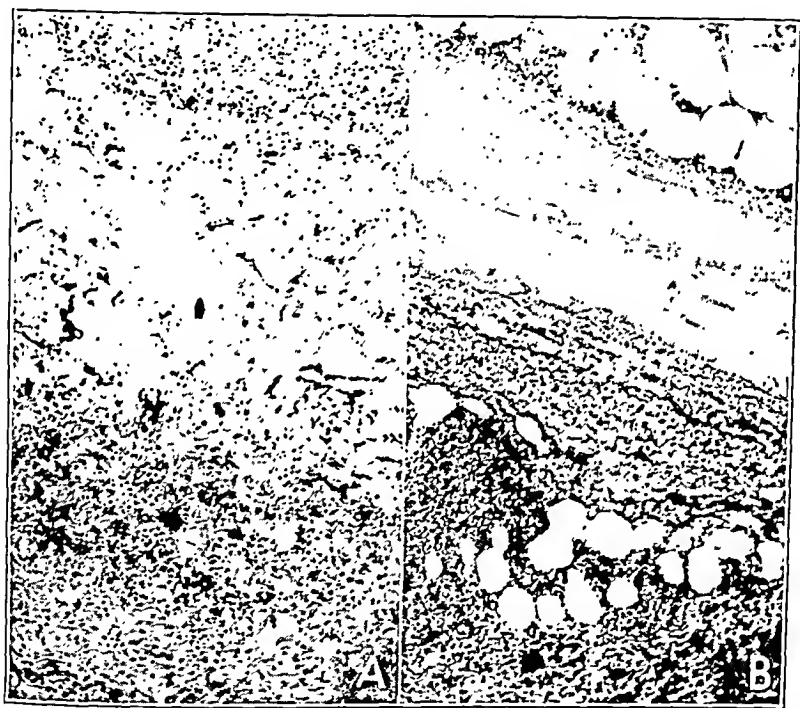


Fig. 2.—Leukocytes localize and concentrate about staphylococci in the skin of the heparinized rabbit in the same way as in a normal animal. *A*, reaction in a normal rabbit four and one-half hours after the subdermal injection of 0.2 cc. of staphylococci. *B*, reaction of rabbit given intravenously a total of 12,000 units of heparin during the interval.

Xylene was applied to the skin of 3 rabbits which had been given heparin to observe the development of the macroscopic evidences of inflammation. These rabbits were given 2,000 units of heparin, and fifteen minutes later xylene was carefully applied to a local area of the skin. The injections of heparin were repeated each forty-five minutes to a total of five injections. Xylene was applied over a second area of skin after the third injection of heparin. Hyperemia and edema occurred fifteen to thirty seconds after the application of xylene. This is the time

in which this change occurs in normal rabbits. From these observations it may be concluded that heparin as used in this experiment does not influence the development of inflammation in the skin of the rabbit.

LOCAL EFFECT OF HEPARIN ON AN INFLAMMATORY REACTION

Heparin when given intravenously over a period of four hours in six equal doses (2,000 units each), as was shown in the previous experiment, apparently has no effect either on the development of macroscopic



Fig. 3.—The local injection of heparin apparently does not influence the localization of leukocytes about staphylococci. Two-tenths cubic centimeter of staphylococci was injected subdermally on the right and the left side. Two hundred units (0.2 cc.) of heparin was injected into the bleb on the right. This quantity of heparin was injected a second time forty-five minutes later and a third time after an additional forty-five minutes. The rabbit was killed two hours after injection of the bacteria. *A*, leukocytic reaction in a rabbit given saline solution. *B*, reaction in the same rabbit when heparin was given.

inflammation or on the localization of leukocytes about the bacteria. To study the local effect of heparin on the development of inflammation, 6 rabbits were given subdermal injections of 0.2 cc. of a heavy saline suspension of staphylococci into two areas on the right and into two areas on the left side of the abdomen. Immediately after injection of

the bacteria, 0.2 cc. of heparin (200 units) was injected into the two blebs on the right and an equal quantity of saline solution was injected into the two blebs on the left. The injections of heparin and saline solution were repeated after forty-five minutes and were given for a third time forty-five minutes later. The rabbits were killed two hours after injection of the organisms. The areas of cutaneous inflammation were removed and fixed in solution of formaldehyde. Histologic sections were prepared and were stained with hematoxylin and eosin.

Macroscopically there appeared to be a more extensive reaction in the areas treated with saline solution than in those treated with heparin. However, microscopically no difference was observed in the number of leukocytes in the areas treated with staphylococci and saline solution as compared with those treated with staphylococci and heparin in the same rabbit (fig. 3). The individual cells in the inflammatory areas in the two groups of animals were studied to see whether there was any variation in the degree of phagocytosis. Heparin, as far as we could determine from a study of these sections, does not affect the phagocytic activity of leukocytes.

OBSERVATIONS ON CAPILLARY PERMEABILITY IN AREAS OF SKIN TREATED BY INJECTION OF HEPARIN

Capillary permeability has been studied after the intradermal injection of a series of different preparations, such as staphylococci, staphylococcus toxin, horse serum broth, tissue extracts and hypertonic solutions of sodium chloride.⁹ Trypan blue localizes and concentrates only during a specific interval where the aforementioned preparations are injected. This interval varies with the different preparations. To study the effect of heparin directly on capillary permeability, 4 rabbits were given intradermal injections of 0.2 cc. of heparin diluted with an equal volume of saline solution (200 units). The heparin was injected two and one-half hours, one hour, thirty minutes and immediately before 10 cc. of a 0.2 per cent solution of trypan blue was given intravenously. Xylene was applied to the skin for a control. The skin was carefully observed for the appearance of the dye. Trypan blue localized and concentrated in the xylene-treated skin in each of the 4 rabbits; however, no dye concentrated in any of the areas into which heparin had been injected.

It is evident from this experiment that heparin as used in these experiments does not affect the permeability of the cells in the rabbit's skin.

9. Rigdon, R. H.: Observations on Capillary Permeability in Areas of Inflammation Produced by Staphylococci, Surgery, to be published. Rigdon, R. H., and Haynes, A.: Observations on Capillary Permeability in Skin of Sensitive Rabbits, J. Lab. & Clin. Med., to be published. Rigdon.^{2b}

COMMENT

The results of this study show that heparin has no effect on capillary permeability, the development of the macroscopic signs of inflammation or the localization of leukocytes in areas of inflammation. It has been shown by other investigators that heparin has no effect on the content of sugar, calcium, uric acid, nonprotein nitrogen or phosphatase in the blood or on the hemoglobin level, red or white cell count or hematocrit reading. It increases the resistance of red blood cells to hypotonic salt solutions, inhibits glycolysis and alters the sedimentation rate. In addition to these changes, all reactions involving complement may be affected because of the inhibitory action on the complement midpieces.¹⁰

The observation that heparin does not influence the localization of leukocytes in areas of inflammation appears to be significant. Although the mechanism of chemotaxis is not understood, many investigators have described the process by which leukocytes localize in areas of inflammation as the result of "a sticking of leukocytes to the endothelial cell." The manner by which the endothelial cells acquire this characteristic is not well understood. It is suggested from this study that this "stickiness" is not the same process as that which occurs in the endothelial cells preceding the formation of thrombi.

Murray^{10a} has presented evidence that heparin will prevent thrombosis in both the portal and the peripheral circulation. The factors which cause the improvement in phlebitis are not well understood; however, Murray said that with heparin limiting the progressive thrombus the inflammatory reaction to the thrombus already present may burn itself out fairly quickly and the symptoms subside. The effect of heparin on thrombosis appears to be on the platelets. Best and his associates¹¹ have observed the localization of platelets on a rough area in a glass tube and have prevented this by adding heparin to the blood.

In considering the effect of heparin on phagocytosis it may be stated that some observers have found that phagocytosis in vitro is increased when heparin is substituted for sodium citrate as the anticoagulant. The latter is thought to be toxic for leukocytes.¹² Studies are now in progress in our laboratory on the effect of varying quantities of heparin on phagocytosis in vitro.

The mechanism of the changes in the endothelial cells of the small blood vessels in areas of inflammation has been discussed in another

10. (a) Murray, G. D. W.: Heparin in Thrombosis and Embolism, *Brit. J. Surg.* **27**:567, 1940. (b) Plass, E. D., and Rourke, M. D.: A New Procedure for Determining Blood Sedimentation Rates, *J. Clin. Investigation* **5**:531, 1928.

11. Best, C. H.; Cowan, C., and McLean, D. L.: Heparin and the Formation of White Thrombi, *Science* **85**:338, 1937.

12. Veazie, L., and Meger, K. F.: Heparin as an Anticoagulant in the Brucella Phagocytic Index Test, *Proc. Soc. Exper. Biol. & Med.* **32**:1616, 1935.

paper.¹ Lange¹³ stated the opinion that the surface tension of the cells in the reticuloendothelial system is changed and that particulate matter sticks to the endothelial cells because of this change in the surface tension.

Mason,¹⁴ in a recent review on heparin, has discussed the effect of this substance on the reticuloendothelial system. He stated:

Von Jansco has employed heparin in experiments to study the mechanism of reticulo-endothelial blockade by colloidal metals. He has shown that storage of these foreign substances by reticulo-endothelial cells takes place in two phases: (1) adsorption on the surface of the cell facilitated by the previous formation of a fibrin network around the particle and (2) vascular storage of the adsorbed particle in the cell. The preliminary process, therefore, resembles that of coagulation and is inhibited by heparin (and several other anticoagulants). A specific means, therefore, is available for blocking this type of behavior of these cells without poisoning or in any other way diminishing their potential activity.

In the present experiments it has been shown that heparin apparently has no effect on the endothelial cells of the small blood vessels in the skin of the rabbit. The variation in the effect of heparin on the function of the cells of the reticuloendothelial system and the endothelial cells lining the small blood vessels in areas of inflammation is interesting.

SUMMARY

Heparin as used in these experiments has no effect on capillary permeability, the macroscopic development of inflammation or the localization of leukocytes in areas of inflammation.

The phagocytosis of staphylococci by polymorphonuclear leukocytes in vivo apparently is not affected by heparin.

13. Lange, F. J.: Role of Endothelium in the Production of Polyblasts in Inflammation, *Arch. Path.* 1:41 (Jan.) 1926.

14. Mason, M. F.: Heparin: A Review of Its History, Chemistry, Physiology and Clinical Applications, *Surgery* 5:451 and 618, 1939.

EFFECT OF HEPATIC DAMAGE ON GASTRIC ACIDITY

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Individual clinical reports (Stevens;¹ Meakins²) are to be found in the literature of decrease or complete absence of gastric acidity in patients with moderate or severe damage to the liver, irrespective of the cause of the damage. One is also familiar with individual analyses of the gastric contents of patients treated for malignant tumor of the stomach or of the kidney in whom large sections of the liver have been damaged secondarily by irradiation; in these studies, too, the recorded values for acidity are definitely lower than the average normal.

It seemed that a systematic study of the effect of damage to the liver on the gastric acidity response was warranted.

PROCEDURE

Dogs were used for these experiments. Damage to the liver was produced experimentally in two ways: (1) by direct high voltage irradiation of the liver and (2) by intragastric administration of carbon tetrachloride in milk. The gastric juice was collected under histamine stimulation by means of a Pavlov pouch (female dogs only) and analyzed.

The experiments with irradiation were performed as follows: The Pavlov pouch was made on the left side of the dog, and control tests of the normal gastric juice were obtained over a substantial period. For direct irradiation the abdomen of the dog was opened under pentobarbital sodium anesthesia; all viscera were blocked off by lead plates, and the liver was exposed to high voltage irradiation for forty-two minutes, the equivalent of three times the skin erythema dose for the human being. The dog received 150 roentgen units each minute. The abdomen was closed, and the gastric acidity was determined at frequent intervals. Each time the values approximated the initial level the experiment was repeated, and this was continued as long as the dog remained in good condition. Biopsy studies were made and blood was drawn for chemical analysis at regular intervals. A complete autopsy was performed on each dog.

From the Department of Medicine, the University of Illinois.

Presented at the Thirteenth Annual Meeting of the Central Society for Clinical Research, Chicago, Nov. 1, 1940.

1. Stevens, A. A.: *The Practice of Medicine*, Philadelphia, W. B. Saunders Company, 1922, p. 424.

2. Meakins, J. C.: *The Practice of Medicine*, St. Louis, C. V. Mosby Company, 1940.

In the carbon tetrachloride experiments the solution was administered intra-gastrically by means of a stomach tube, 1 cc. per 7 pounds (3 Kg.) of body weight three times weekly as long as the dog remained in good physical condition. Studies of the gastric juice, analyses of the blood and analyses of biopsy sections of the liver of each dog were made. A control experiment was performed in which radiation was applied over the muscles of the leg of the dog.

RESULTS

Irradiation.—Table 1 shows a schedule for the dogs treated by direct irradiation.

TABLE 1.—*Schedule of Dogs Treated by Irradiation*

Dog	Date	Weight, Pounds	Duration of Experi- ment, Months	No. of Treat- ments *	Dose in Roent- gens *	Condition of Dog 24 Hours Before Death	Liver	
							Biopsy	Autopsy
2	12/13/37	26	16	7	35,700	Good	Atrophy	Granular necrosis
13	11/28/38	22	15	10	63,000	Good	Atrophy	Granular necrosis
19	2/22/39	30	19	4 E 6 L	25,200 E 37,800 L	Good	Atrophy	
20	4/ 5/39	26	15	8	50,400	Good	Atrophy	Granular necrosis
23	3/14/40	26	6	2	12,600	Good	Atrophy	

* E following a number indicates that that number of radiation treatments or of roentgens was applied to the extremity. L following a number indicates that that number of radiation treatments or of roentgens were applied to the liver.

TABLE 2.—*Maximal Acidity (Dogs 2, 13 and 20)*

Dog	Treat- ments	Before Irradiation		After Irradiation	
		Free Acid, mEq.	Total Acid, mEq.	Free Acid, mEq.	Total Acid, mEq.
2	7	120	152	63.2	100.68
13	9	109.76	121.68	55.0	86.0
20	7	122.0	138.8	62.0	107.0

Gastric Acidity: In dogs 2, 13 and 20 (table 2) changes in the acidity were noted. Within forty-eight to seventy-two hours after each treatment there was evident an initial increase in the gastric acidity (free and total) over the pre-treatment level, and then a gradual decrease followed. If additional radiation treatments were administered the acidity curve climbed to the previous level and remained at that point. Subsequent irradiation exaggerated the depression of gastric acidity. With each additional treatment the acidity curve was delayed more and more in its return to a previous level, and in the terminal stage the dog was not only incapable of producing as much acidity as previously but actually produced less. In other words, a definite low level was established. Dogs 19 and 23 are now under observation and have received six and two treatments respectively. In figures 1 and 2 is demonstrated the behavior of gastric acidity after direct irradiation of the liver, expressed in milliequivalents per thousand cubic centimeters of gastric juice.

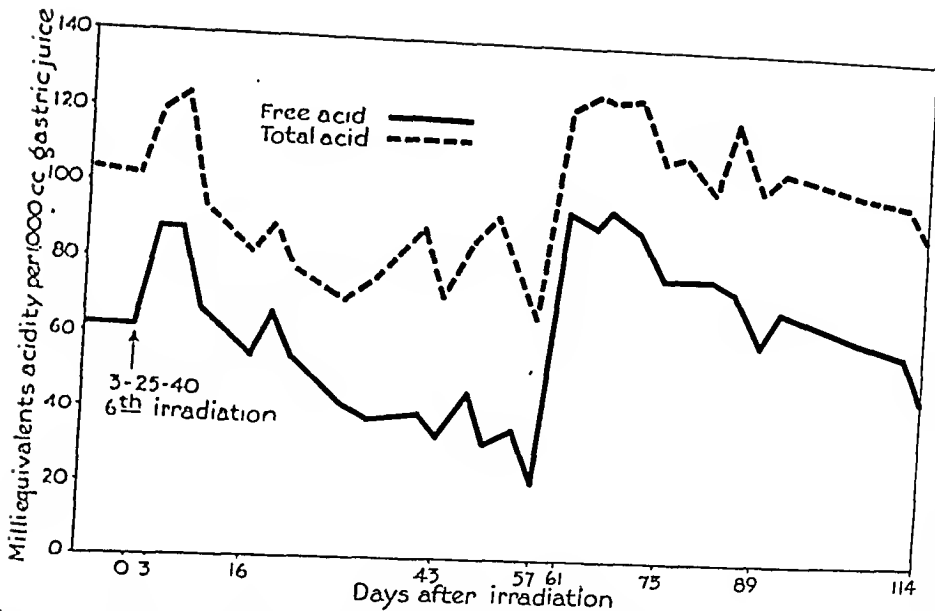


Fig. 1.—Behavior of gastric acidity after direct irradiation of the liver of dog 19.

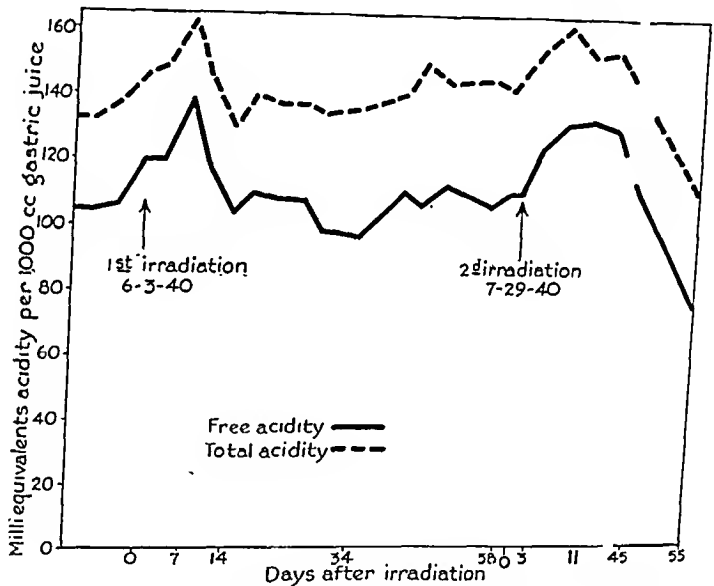


Fig. 2.—Behavior of gastric acidity after direct irradiation of the liver of dog 23.

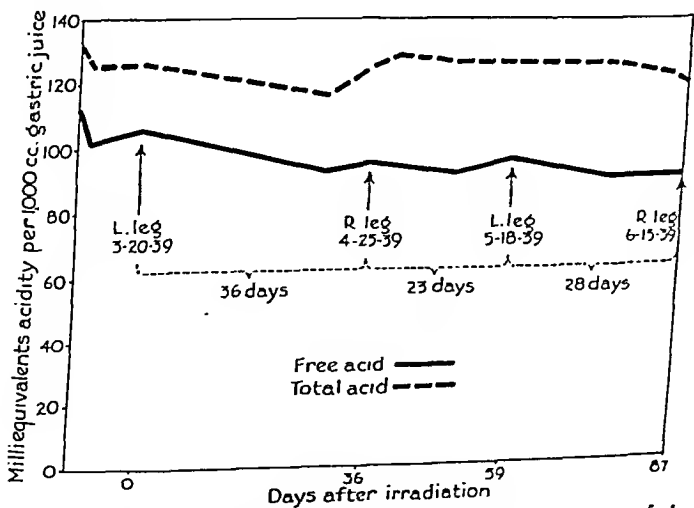


Fig. 3.—Response of gastric acidity to irradiation of the muscles of the extremity (dog 19).

Sternberg⁸ expressed the belief that the disease is an atypical form of tuberculosis, although this was opposed vigorously by Reed,³ who maintained the process is an infective granuloma of unknown cause. Fraenkel and Much⁸ (1910) and Bunting and Yates⁹ (1913) reported that they found specific causative organisms.

Gordon¹⁰ in 1932 described a test, positive in 70 per cent of the cases, which consisted of intracerebral injection of a broth suspension of diseased lymph nodes into rabbits and guinea pigs. A syndrome consisting of spastic paralysis, ataxia, retraction of the head, fits and loss of weight was produced. He was convinced that a virus was responsible for the disease. In 1938, four different workers¹¹ showed that the eosinophils in tissue affected by Hodgkin's disease were responsible for the encephalitic reaction of the animals and that the same reaction can be produced by other tissues containing eosinophils. The Gordon test is a valuable confirmatory test when accompanied by histologic examination, as shown recently by Steiner,¹² who found the test positive in 73.9 per cent of 299 recorded cases of histologically proved Hodgkin's disease and falsely positive in only 1.77 per cent of 452 control cases.

In 1939 Parsons and Poston¹³ reported a group of 4 cases of human brucellosis in which the histologic study of lymph nodes and autopsy material revealed the characteristics of typical Hodgkin's disease. Recently at the same hospital Forbus and Gunter¹⁴ studied autopsy material from 4 additional cases of typical Hodgkin's disease, with recovery of the *Brucella* organism in all. Poston and Parsons¹⁵ reported cultures of *Brucella* from the lymph nodes of 10 of 19 patients with Hodgkin's disease.

The present paper analyzes 54 cases of histologically proved cases of Hodgkin's disease observed at the University of Virginia Hospital in the past fifteen years. Biopsy was performed in 51 cases and autopsy

8. Fraenkel, E., and Much, H.: *Ztschr. f. Hyg. u. Infektionskr.* **67**:159, 1910.

9. Bunting, C. H., and Yates, J. L.: *Cultural Results in Hodgkin's Disease*, *Arch. Int. Med.* **12**:236 (Aug.) 1913.

10. Gordon, M. H.: *Rose Research on Lymphadenoma*, Bristol, John Wright & Sons, Ltd., 1932.

11. Edward, D. S.: *Lancet* **1**:936, 1938. King, D. P.: *St. Thomas's Hosp. Rep.* **3**:68, 1938. McNaught, J. B.: *Gordon Test for Hodgkin's Disease: Reaction to Eosinophils*, *J. A. M. A.* **111**:1281 (Oct. 1) 1938. Turner, J. C.; Jackson, H., Jr., and Parker, F.: *Am. J. M. Sc.* **195**:27, 1938.

12. Steiner, P. E.: *Reliability and Significance of Gordon Test in Hodgkin's Disease*, *Arch. Path.* **31**:1 (Jan.) 1941.

13. Parsons, P. B., and Poston, M. A.: *South. M. J.* **32**:7, 1939.

14. Forbus, W. D., and Gunter, J. U.: *South. M. J.* **34**:376, 1941.

15. Poston, M. A., and Parsons, P. B.: *J. Infect. Dis.* **66**:86, 1940.

in 4. About 20 other cases were not included because the histologic changes were inconclusive or the diagnosis was merely clinical. One case in which Hodgkin's disease was diagnosed on biopsy of a cervical lymph node is omitted; this will be reported separately,¹⁶ as the patient died three months later of generalized torulosis.

INCIDENCE

Race.—Hodgkin's disease has been reported to attack every race and nearly all nationalities. The reports of cases in America indicate that the distribution has been predominantly among the white and American born. Goldman¹⁷ reported an incidence of 6.6 per cent Negroes in a group of 212 patients with Hodgkin's disease.

In our series the condition occurred in 45 white persons (83.3 per cent) and 9 Negroes (16.7 per cent). Over a period of many years the average admission rate of Negroes at this hospital has been 15.6 per cent.

Sex.—The disease is more prevalent in men than in women. Wallhauser⁷ collected 1,447 cases from the literature and found the incidence to be 70 per cent in men and 30 per cent in women.

In our group there were 32 men (59.3 per cent) and 22 women (40.7 per cent).

Age.—Hodgkin's disease may occur at any age. Smith¹⁸ collected 5 cases in which the onset was before the sixth month of age. A number have been recorded in which the condition developed in the seventh and eighth decades of life. In the greatest number of cases the onset occurred in the third decade of life.

The youngest patient in our series was 4 and the oldest 70. The greatest number of the patients were in the third decade of life; the incidence of the disease was fairly well distributed over the other decades except the sixth, in which it was low, and the seventh, in which it was higher than in any except the third (chart).

PREDISPOSING FACTORS AND POSSIBLE CAUSES

There were no demonstrable predisposing factors in any of the cases studied. Heredity, environment, occupation and food appeared to play no important part. The majority of the patients were ward patients, but there were 2 physicians' wives and 1 hospital intern in

16. Morton, C. B.; Derrick, W. A., and Burger, R. E.: Torula Infection: A Review and Report of Three Cases, to be published.

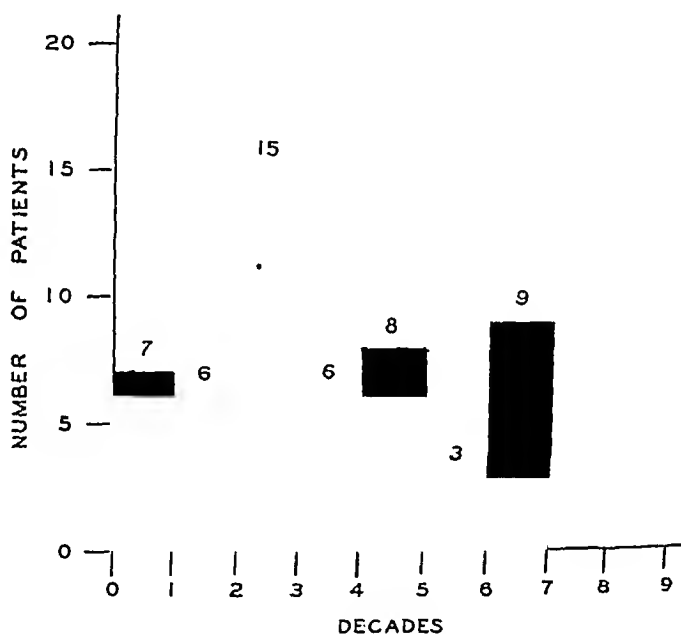
17. Goldman, L. B.: Hodgkin's Disease: Analysis of Two Hundred and Twelve Cases, J. A. M. A. **114**:1611 (April 27) 1940.

18. Smith, C. A.: J. Pediat. **4**:12, 1934.

the group. There was no familial history of Hodgkin's disease. McHeffey and Peterson¹⁹ reported the occurrence of Hodgkin's disease in 2 brothers almost simultaneously.

Roentgenograms of the chest in 3 cases revealed scarring and calcification consistent with old healed tuberculosis; in 3 additional cases there was suspicion of activity, and in 1 case there was death from concomitant pulmonary and miliary tuberculosis and Hodgkin's disease. Thus in 12.9 per cent of the cases there was healed or active tuberculosis.

Of the 54 cases, cultures of the blood were made in 3 and of the lymph nodes in 2. In 1 case the culture of the blood was positive for *Brucella*.



Age incidence in 54 cases of Hodgkin's disease.

CHIEF COMPLAINTS AND SYMPTOMS

Swelling of the glands of the neck, weakness, fatigue, loss of weight, cough, dyspnea and backache were the commonest complaints on admission to the hospital. Table 1*A* records the chief complaint and table 1*B* the symptoms present on admission in 44 cases; in 10 cases there were no symptoms except the swelling of glands.

The average time between the onset of symptoms and entry into the hospital in 52 cases was ten and one-half months. There was no record of the duration of the disease before admission in 2 cases.

19. McHeffey, G. J., and Peterson, R. F.: Hodgkin's Disease Occurring Simultaneously in Two Brothers, *J. A. M. A.* **102**:521 (Feb. 17) 1934.

TABLE 1.—*Chief Complaints and Symptoms in Cases of Hodgkin's Disease*

A. The Chief Complaint That Brought 54 Patients to the Hospital				B. The Most Common Symptoms Prior to Hospitalization in 44 Cases (In 10 Cases There Were No Symptoms)		
Complaint	Patients	Per Cent		Common Symptoms	Cases	Per Cent
Swelling of the glands of the neck.....	31	57.4		Weakness.....	26	48.2
Fatigue and weakness.....	5	9.3		Loss of weight.....	10	35.2
Pain in the back and the legs.....	5	9.3		Cough.....	13	21.1
Cough, dyspnea and sore throat.....	3	5.6		Fatigue.....	9	16.6
Abdominal pain.....	3	5.6		Anorexia.....	8	14.8
Mass in the abdomen.....	2	3.7		Pain in the back and the legs.....	8	14.8
Generalized superficial glandular enlargement.....	1	1.8		Nausea.....	7	12.9
Enlargement of the inguinal glands.....	1	1.8		Nervousness.....	6	11.1
Pain in the eyes and head.....	1	1.8		Edema.....	6	11.1
Cutaneous lesions.....	1	1.8		Dyspnea.....	5	9.3
Tuberculosis.....	1	1.8		Fever.....	5	9.3
				Headache.....	4	7.4
				Abdominal pain.....	4	7.4
				Nausea and vomiting.....	3	5.6
				Night sweats.....	2	3.7
				Sore throat.....	2	3.7
				Pain in the neck.....	2	3.7
				Pruritus.....	2	3.7

CLINICALLY OBSERVED LOCALIZATION

Although the disease is usually generalized, with widespread involvement of the reticuloendothelial system, definite areas of localization are observed clinically. A characteristic of the disease in the early stages is that unilateral lymphatic areas are attacked more frequently than symmetric areas. The lymph nodes of the neck were involved first in two thirds of the cases. Table 2*A* gives the regions first involved in this group, determined by palpation, roentgenograms and surgical exploration. Table 2*B* gives the frequencies of involvement of lymph nodes, tissues and organs during the course of the disease.

Mediastinum.—Involvement of the mediastinum, as evidenced in roentgenograms by widening, nodular protrusions of enlarged glands and actual infiltration of the lungs, was present in 55.5 per cent of the cases. In 2 cases the mediastinal nodes were apparently the first of the body structures to be involved. There was involvement of mediastinal nodes in all 4 of the patients who came to autopsy.

Stomach.—Sherman²⁰ in 1938 collected 75 cases of Hodgkin's disease in the gastrointestinal tract from the literature, and in about a third of these cases there was involvement of the stomach.

The stomach and regional lymph nodes were involved in 2 cases of our series. In each instance a roentgenogram revealed a large filling defect in the stomach, and at exploration a large mass was found in the stomach, with involvement of regional lymph nodes. These were thought to be cases of inoperable carcinoma till biopsy of the regional nodes revealed Hodgkin's disease.

Spleen.—During the course of the disease the spleen was observed clinically to be enlarged in 33.3 per cent of the cases. Of the 4 patients who came to autopsy, 3 had involvement of the spleen, and 2 of these had palpably enlarged organs.

Desjardins and Ford²¹ (1923) noted splenomegaly in only 14.9 per cent of 135 cases. Boyd²² stated that 75 per cent of the cases show splenomegaly.

Liver.—The liver was palpable in 20 (37 per cent) of the cases. This is somewhat lower than the 60 per cent given by Ziegler²³ and

20. Sherman, E. D.: Gastro-Intestinal Manifestations of Lymphogranulomatosis (Hodgkin's Disease), *Arch. Int. Med.* **61**:60 (Jan.) 1938.

21. Desjardins, A. V., and Ford, F. A.: Hodgkin's Disease and Lymphosarcoma, *J. A. M. A.* **81**:925 (Sept. 15) 1923.

22. Boyd, W.: *The Pathology of Internal Diseases*, Philadelphia, Lea & Febiger, 1934.

23. Ziegler, K.: *Die Hodgkinsche Krankheit*, Jena, Gustav Fischer, 1911.

TABLE 2.—Cases in Which Involvement of Certain Organs Was Shown

A. Region First Involved			B. Region Involved at Some Stage of the Disease		
Organ or Nodes	Cases	Per Cent	Organ or Nodes	Cases	Per Cent
Left cervical nodes.....	13	27.8	Left cervical nodes.....	44	81.5
Right cervical nodes.....	14	25.9	Right cervical nodes.....	37	68.5
Cervical nodes on both sides.....	7	12.9	Axillary nodes.....	27	50.0
Inguinal nodes.....	6	11.1	Inguinal nodes.....	20	37.0
Axillary nodes.....	3	5.6	Epitrochlear nodes.....	1	1.8
Abdominal nodes, liver and spleen.....	3	5.6	Mediastinum.....	30	55.5
Generalized superficial glands.....	2	3.7	Liver.....	20	37.0
Mediastinum.....	2	3.7	Spleen.....	19	35.2
Stomach and regional nodes.....	2	3.7	Abdominal nodes.....	8	14.8
			Stomach and regional nodes.....	2	3.7
			Bone.....	4	7.4
			Skin.....	2	3.7
			Eye and retrobulbar tissues.....	2	3.7

the 50 per cent given by Boyd.²² The liver was involved in 2 of the 4 cases in which there was an autopsy and in 1 in which surgical exploration was done. There was clinical icterus in 2 (3.7 per cent) of the cases; this was in agreement with 4.2 per cent in Goldman's¹⁷ 212 cases.

Skin.—Cutaneous involvement was proved histologically in 2 cases. In the first it was associated with generalized superficial glandular enlargement; in the second, with involvement of the liver proved by biopsy. Puritus was present during the course of the disease in 10 (18.5 per cent) of the cases. .

Bone.—In 4 of the cases (7.4 per cent) there was roentgen evidence of osseous involvement. Goldman¹⁷ reported osseous involvement in 6.6 per cent of 212 cases and Craver and Copeland²⁴ in 15.7 per cent of 172 cases. The bones involved in our series were more commonly the vertebrae, less often the pelvic bones, sacrum and ribs. Biopsy of involved bone of 2 of the patients showed tissue typically affected by Hodgkin's disease. Three other patients complained of moderately severe pain in the back and hips at some time during the course of the disease, but roentgenograms were never taken.

BLOOD PICTURE

Opinions as to the blood picture in Hodgkin's disease differ widely. Bunting²⁵ emphasized certain changes in the blood count and blood smear, but these are variable. Steadily progressive anemia of the hypochromic type is usually found. In this series 32 (59.3 per cent) patients had a leukocyte count above 8,000. The two highest leukocyte counts were 68,300 and 54,000, with polymorphonuclears predominant; eosinophils were not present in the blood smear in the first instance and were 2 per cent in the second. In both the leukocytosis was accompanied by rather severe secondary anemia. Both the patients had superficial glandular enlargement plus bony involvement. The leukocyte count of 1 patient receiving no treatment was 2,600. Five patients receiving roentgen therapy had their previously normal leukocyte counts depressed below 4,000. The leukocyte counts of the remainder of the patients were within the normal range.

Eosinophilia has long been stressed as a characteristic finding. Goldman¹⁷ and Baker and Mann²⁶ observed eosinophilia in 20 per cent of their cases. In our series there was eosinophilia (5 per cent

24. Craver, L. F., and Copeland, N. M.: Changes in Bone in Hodgkin's Granuloma, *Arch. Surg.* 28:1062 (June) 1934.

25. Bunting, C. H.: *Bull. Johns Hopkins Hosp.* 25:173, 1914.

26. Baker, C., and Mann, W. N.: *Guy's Hosp. Rep.* 89:83, 1939

or more) in 20.3 per cent of the cases. The highest was 25 per cent, in the case of Hodgkin's disease of the skin associated with superficial glandular disease.

OCCURRENCE OF FEVER

In 1887 Pel²⁷ and Ebstein²⁸ described periodic bouts of fever with remissions in the disease process. Of the 54 patients in our series, all but 5, whose disease was in an early stage, were pyrexia when observed. A continued or swinging pyrexia with temperatures from 100 to 104 F. was much more common than the classic Pel-Ebstein variety, which occurred in only 8 (14.8 per cent) of the patients under observation.

DURATION OF LIFE

Hodgkin's disease may be rapidly fatal or slowly progressive. Two of the patients whose disease ran the shorter course lived about three months after the onset of symptoms; the patient who lived longest died eight years, eight months after the onset. The average duration of life of 41 patients followed up and known to be dead was twenty-six months, dating from the onset of symptoms. Four patients are thought to be dead, but a follow-up could not be obtained. Nine patients known to be alive have been living an average of twenty-nine and five-tenths months at the time of writing. In Goldman's¹⁷ 212 cases the average duration of life was about thirty-two months; in Baker and Mann's²⁸ 65 cases it was about eighteen months. Craver²⁹ reported periods of survival of five years or more in 12 per cent of 125 proved cases of Hodgkin's disease. In our series 3 patients (5.6 per cent) are known to have lived longer than five years.

SECONDARY CAUSES OF DEATH

In 28 of the known fatal cases the mode of death is known and is given in table 3.

Terminal exhaustion, anemia and pyrexia were mentioned most often, being present in 21 cases.

Death due to respiratory failure with signs of pulmonary disease or mediastinal compression occurred in 6 cases. One patient died on the operating table shortly after an attempt to decompress the mediastinum because of marked respiratory difficulty.

In 1 case there were concomitant Hodgkin's disease and pulmonary and military tuberculosis.

27. Pel, P. K.: *Berl. klin. Wchnschr.* 24:644, 1887.

28. Ebstein, W.: *Berl. klin. Wchnschr.* 24:565, 1887.

29. Craver, L. F.: *Am. J. M. Sc.* 188:609, 1934.

In many there was overlapping of the terminal symptoms, and it was rather difficult to select the cause of death.

RESULTS OF TREATMENT

The methods of treatment in this series of cases are given in table 4. The larger number of the patients (41) were given roentgen therapy alone to the involved areas. A few had surgical or radium treatment alone; 2 had combined surgical and roentgen therapy, and 5 received no treatment.

In the group known to be dead the average duration of life was much greater in those receiving treatment, regardless of the type of

TABLE 3.—*Mode of Death in Twenty-Eight Cases of Hodgkin's Disease*

Type	Cases	Per Cent
Respiratory failure.....	6	21.4
Exhaustion, anemia and pyrexia.....	21	75.0
Miliary tuberculosis.....	1	3.6

TABLE 4.—*Results of Treatment **

Type of Therapy	Patients (41) Known to Have Died		Patients (9) Still Alive	
	Patients	Average Length of Life (Mo.)	Patients	Average Living Time at Time of Writing (Mo.)
Roentgen alone.....	30	28.1	9	29.5
Surgical alone.....	5	28.2
Radium alone.....	1	30.0
No treatment.....	5	10.4

* Of the patients who were not followed up, 2 received roentgen therapy alone and 2 combined surgical and roentgen therapy.

therapy, than in those not receiving treatment. Those receiving some form of therapy lived twenty-eight to thirty months; those not receiving treatment lived only ten and four-tenths months.

In 9 living patients receiving repeated irradiation of involved tissues the duration of life at the time of writing was already twenty-nine and five-tenths months. Roentgen irradiation of the entire lymphatic system has not been tried at this hospital. Blood transfusions and general therapeutic measures have been valuable adjuvants in building up the patients.

Most roentgen therapists use repeated local application of irradiation. Jacox, Peirce and Hildreth³⁰ in surveying the clinical results

30. Jacox, H. W.; Peirce, C. B., and Hildreth, R. C.: *Am. J. Roentgenol.* 36:165, 1936.

of this form of treatment in 161 cases of Hodgkin's disease over a decade, were convinced that roentgen therapy induced definite extension of life and that systemic irradiation was proving more effectual in prolonging life than repeated local irradiation.

Regardless of the type of therapy, Hodgkin's disease has proved an almost universally fatal malady in the proved cases. There are a few isolated reported cures, but as to most of these there is a question of correct diagnosis or of adequate follow-up. A few cases have been reported in which the patient lived twenty years or more, and Jackson³¹ recorded a case in which there was recurrence of nodes removed surgically after a lapse of twenty-six years.

SUMMARY

We have analyzed 54 cases of histologically proved Hodgkin's disease seen at the University of Virginia Hospital in the past fifteen years. In discussing the clinical features, we have compared our figures with others occurring in the literature.

No data relating to causation are presented. In 1 case among 3 studied by culture of the blood, *Brucella* was isolated.

Enlargement of the cervical glands is commonly the first sign and is followed later in most instances by involvement of superficial and mediastinal nodes, accompanied by swinging or sustained pyrexia, usually not of the Pel-Ebstein type.

The average time of survival from the onset of the first symptom was twenty-six months. Treatment in most cases consisted of repeated roentgen irradiation of involved tissues aided with blood transfusions and general therapeutic measures. Treated patients have on the average survived nearly three times as long as untreated patients.

Dr. W. Ansell Derrick, of the department of pathology of the University of Virginia, assisted in reviewing the histologic slides.

31. Jackson, H., Jr.: *M. Clin. North America* 21:361, 1937.

PREOPERATIVE MANAGEMENT OF GASTROJEJUNOCOLIC FISTULA

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The immediate mortality rate after surgical intervention in the treatment of well developed gastrocolic fistula is disturbingly high, and yet the prognosis for the disease if treated by medical means alone is exceedingly poor. Nearly all patients treated medically die of progressive inanition, avitaminosis or intercurrent infection. Verbrugge¹ reported a series of 20 cases in which 5 patients died after operation; the mortality rate was thus 25 per cent. Loewy² collected reports of 63 cases; the operative mortality rate in this group was 27 per cent. Allen³ reported 8 cases with 2 deaths; Lahey and Swinton⁴ reported an immediate mortality rate of 63 per cent in 8 cases and Rife⁵ a mortality rate of 20 per cent in 14 cases. A high mortality rate seems to accompany any type of operation performed in one stage, regardless of the technic employed or the quality of the postoperative management.

The first report of a spontaneous communication between the stomach and the colon was made by Haller⁶ in 1755. Prior to 1903, when Czerny² reported the first case of gastrojejunocolic fistula after gastroenterostomy, in most of the 70 cases reported the anomaly was caused by carcinoma of the stomach or the colon. Since that time the increasing use of gastroenterostomy in the treatment of duodenal ulcer has resulted in the establishment of a communication from the stomach to the jejunum and colon in many cases. When such a fistula occurs now, it is usually presupposed that gastroenterostomy has been performed—in most cases, years before for benign duodenal ulcer—and that an eroding, adherent gastrojejunal ulcer developed. Such a communication

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1. Verbrugge, J.: Gastrojejunocolic Fistulas, *Arch. Surg.* **11**:790-808 (Nov.) 1925.

2. Cited by Pfeiffer and Kent.¹¹

3. Allen, A. W.: An Aseptic Technic Applicable to Gastrojejunocolic Fistula, *Surgery* **1**:338-348 (March) 1937.

4. Lahey, F. H., and Swinton, N. W.: Gastrojejunal Ulcer and Gastrojejunocolic Fistula, *Surg., Gynec. & Obst.* **61**:599-612 (Nov.) 1935.

5. Rife, C. S.: Gastrojejunocolic Fistula, *Am. J. Surg.* **40**:73-88 (April) 1938.

6. Haller, cited by Tynes, A. L., and Cole, F. L.: Gastrojejunocolic Fistula with Report of Three Cases, *Mil. Surgeon* **86**:113-121 (Feb.) 1940.

after gastroenterostomy for gastric ulcer is rare and seldom occurs in women. Gastrojejunocolic fistula apparently occurs in 0.1 to 0.2 per cent of the cases in which gastroenterostomy is performed and in about 10 per cent of the cases in which gastrojejunal ulcer develops.

PURPOSE AND MATERIAL OF STUDY

It is the purpose of this study to present a review of 49 consecutive cases of well developed gastrojejunocolic fistula in which operation was performed at the Mayo Clinic from 1930 to 1939, inclusive. Cases of so-called impending fistula are not included. All operations were performed in one stage, but many different types of corrective measures were used; these have been described by Walters and Clagett.⁷ Besides the one stage operation, the only other constant factor in these cases was the preoperative management and preparation of the patient. Emphasis will therefore be placed on the preoperative management and the effect of this on the immediate operative mortality.

Factors which enter into the prevention of such fistulas will not be mentioned, except to emphasize that a great part of the rationale of preoperative management of fistula is based on the knowledge that the disease is a manifestation of a long-standing debilitating process. Furthermore, most of the patients are not cooperative with medical treatment, as evidenced by the fact that in most of the cases reported here the duodenal ulcer, then the gastrojejunal lesion and, finally, the gastrocolic fistula, developed while the patient was receiving medical care. It is apparent also that the inanition and avitaminosis resulting from such lesions may be productive of postoperative peritonitis, tetany and pneumonia.

DATA ON PATIENTS

None of the 49 patients of this series were women. All patients had undergone gastroenterostomy for duodenal ulcer. In 40 cases posterior gastroenterostomy alone was the primary procedure. In 8 cases, previous acute perforation of a duodenal ulcer had occurred; the opening was closed, and posterior gastroenterostomy was performed then or later. The duodenal ulcer of 1 patient had been excised and posterior gastroenterostomy performed; the usual symptoms of duodenal ulcer had occurred. Of the 49 patients, only 7 had cooperated in their medical treatment; the rest had been listed as poorly cooperative or non-cooperative.

In 14 cases in this series, further operations had been performed on the stomach after the initial gastrojejunostomy and prior to the formation of the fistula. These operations, which were usually made necessary by the formation of an anastomotic ulcer, consisted preponderantly of

⁷ Walters, W., and Clagett, O. T.: Gastrojejunocolic Ulcer and Fistula, *Am. J. Surg.* 46:94-102 (Oct.) 1939.

some type of plastic or short-circuiting procedure. The operations were almost always futile, unless some type of gastric resection was performed. Even then the fistula ultimately formed. Whether early gastric resection would have forestalled the final penetrating ulcer cannot be said definitely. One patient had undergone four such intervening operations. Two years after the initial gastrojejunostomy, an enteroanastomosis for correction of a malfunctioning stoma was carried out. A year later an exclusion operation of the Devine type was performed in an attempt to control the anastomotic ulcer. In five months the gastrojejunal ulcer was excised without changing the continuity of the gastrointestinal tract. Nine years later a Billroth I operation of the von Haberer type was performed. Two patients required three such intervening operations; 4 had two, and the remaining 7 patients had one operation between the gastroenterostomy and the final operation.

The necessity for repairing the gastrojejunocolic fistula occurred on an average five years after the initial gastroenterostomy, but in 1 case twenty-nine years had passed before symptoms of fistula developed, and in another case barely a year had passed before a well developed gastrojejunocolic fistula was demonstrated. The youngest patient to have a fistula was 27 years of age. He had been aware of the presence of a duodenal ulcer since the age of 15 and had had symptoms of gastrocolic fistula for four months prior to registration at the clinic. Gastroenterostomy had been performed when he was 18 years of age, and he had had two subsequent operations for ulcer at the anastomosis. The oldest patient was 65 years of age when repair of the fistula was attempted. The average age of the patients was about 46 years.

SYMPTOMS

The symptoms heralding the development of gastrojejunocolic fistula usually are easily distinguished. The history and the aspect of the patient are rather typical. The story is one of long-standing recurrent distress from the ulcer, for which gastroenterostomy first had been performed and occasionally had been followed by other operative attempts to control the continued distress caused by the anastomotic ulcer. A gastrojejunocolic fistula cannot develop unless the anastomotic ulcer is present first. The severe pain of anastomotic ulcer and a shift of pain from the epigastrium to the umbilical region and left side of the epigastrium occur. In the absence of a definite fistula, symptoms of colonic irritation are suggestive of an impending break into the colon. A roentgen diagnosis of gastrojejunal ulcer prior to establishment of a communication between the stomach and the colon was made in a large percentage of cases in this series. In about 30 per cent of the cases the patient had had hemorrhages of various degrees of severity from the anastomotic ulcer before development of the fistula.

With establishment of the fistula the pain usually ceases and diarrhea begins. The stools are usually watery and copious and finally contain large quantities of undigested food which has recently been ingested. Occasionally the patient has a ravenous appetite, but usually there is anorexia with marked loss of weight. Hemorrhage occurred after development of the fistula in 10 per cent of our cases; in 30 per cent of these it occurred before final establishment of the fistula. Frequently patients with gastrojejunal fistula complain of a bad taste in the mouth, and about 60 per cent of them will notice foul-smelling eructation. One patient belched while lighting a cigaret and was amazed to see a flare of flame. Fecal vomiting, which usually occurs late in the course of the disease, is found in 15 per cent of the cases. Dehydration, emaciation and nutritional edema may develop rapidly, depending on the size of the opening and the quality of the diet. If the symptoms are allowed to progress unchecked by reparative procedures, pellagra may develop. In a large percentage of cases avitaminotic manifestations of lesser degree will develop.

On admission to the hospital for preoperative preparation, only 13 of the 49 patients were in good condition; 8 more were in relatively good condition. Twenty-seven had edema of the limbs, the abdomen or the face in varying degrees; marked emaciation and loss of weight were the rule. Twenty patients showed some evidence of avitaminosis, and 9 had associated mental derangement, dermatitis and glossitis. One patient had definite carpopedal spasm. Serious anemia was present in only a few cases; in these cases hemorrhage had occurred.

DIAGNOSIS

The diagnosis of a well developed gastrojejunal fistula when the history and the aspect of the patient are kept in mind is not difficult. In about a fourth of the cases an inflammatory mass can be palpated in the epigastrium or just above the umbilicus. If roentgen studies are to be made, the method of choice includes a barium sulfate enema. In these 49 cases a well developed fistula was present, yet a positive roentgen diagnosis was made in only 13 of the 40 cases in which roentgenograms of the stomach were made. In 25 cases in this series roentgen examination of the colon was made after a barium sulfate enema had been given; the fistula was demonstrated in each instance.

The laboratory studies with the exception of the chemical findings of the blood and the values for serum protein were not remarkable. A slight hypochromic anemia was usually present. In cases in which repeated hemorrhage had occurred, rather serious anemia prevailed. The gastric acidity was slightly elevated in those cases in which intervening partial gastric resection had not been performed for gastrojejunal ulcer, but the total acidity was never more than 100 or the free hydrochloric acid ever more than 65 (Töpfer's method). The usual test meal

revealed a total acidity of about 50 and free hydrochloric acid of 35 to 40. In the cases in which gastric resection had been performed, the total acidity and free hydrochloric acid were markedly lowered. The total protein was determined in 17 cases; in 11 the value was less than 5 Gm. per hundred cubic centimeters of serum at the time of admission. The albumin-globulin ratio was disturbed to some extent in most of the cases. The level of vitamin C in the plasma was not determined in enough cases to warrant definite conclusions. However, the test was carried out in 7 cases. Normal values range from 0.9 to 1.5 mg. per hundred cubic centimeters of plasma; in only 1 of the 7 cases did the level of vitamin C fall within normal limits. In the remainder it varied from 0.49 to 0.8 mg. per hundred cubic centimeters.

PREOPERATIVE PREPARATION AND ITS EFFECT ON OPERATIVE MORTALITY

Preparing these patients thoroughly and adequately for the extensive operative procedures necessary to effect a cure presents a formidable problem. As can be seen, the clinician is dealing with a patient who is surviving with difficulty the ravages of inanition and whose reserve for reparative processes after operation is low. Furthermore, the chemical constituents of his blood are out of balance, and his courage and will to live are at low ebb because of the nature of his disease. The surgeon cannot assume the responsibility of an attempt at closure of the fistula until the patient has regained some measure of strength and reserve, and the grave risk attending surgical procedures on such patients is obvious.

In this series of 49 cases there were 18 postoperative deaths, a mortality rate of 36.7 per cent. As already pointed out, cases in which the surgeon noted an impending fistula and in which the mortality rate was greatly lower were not included. In order to determine to some degree the effect of preoperative preparation of the patients on the operative mortality rate, they were divided into three groups.

Group 1.—This group consisted of 13 patients (26.5 per cent of the series) who seemed in good condition on admission to the hospital. Seven were considered such good risks that operation was performed on them the day after admission. The chemical constituents of the blood, the serum protein and the results of routine blood studies were normal in 11 cases. None of the patients in this group showed clinical evidence of avitaminosis, but 5 had edema of either the ankles or the abdomen. Because of these findings, the hazards of the proposed operation were thought to be greatly less and meticulous preoperative preparation was thought unnecessary. Yet this group of patients in relatively good condition ultimately did far worse after operation than

another group who were so ill on admission that careful preparation was necessary before they could be subjected to operation.

The average stay in the hospital before operation was less than two and a half days. In no case was an attempt made to cleanse the colon with repeated enemas, to give vaccine intra-abdominally or to administer low residue or residue-free diets. Three of the patients were given fluids by the intravenous route before operation, usually a 5 per cent solution of dextrose in distilled water. No attempt was made to increase the body's store of vitamins. Eight of 13 patients died after operation (a mortality rate of 61.5 per cent). Nearly half (44.4 per cent) of the deaths in the entire series occurred in this small group.

Because of the high operative mortality rate in this small group of cases in which preoperative preparation was not given, it was interesting to study the effect of preoperative preparation on the mortality rate. This study was undertaken with groups 2 and 3 to determine if possible what method of preparation would give the patient the best chance of cure.

Group 2.—This group consisted of the remaining 36 patients, who were considered more thoroughly prepared for operation. Ten died (a mortality rate of 27.7 per cent). A little more than half (55.6 per cent) of the deaths in the entire series were in this group, yet the mortality rate (27.7 per cent) was definitely lower than that of the whole series (36.7 per cent).

The average preoperative stay in the hospital was seven and seven-tenths days. When chemical examination of the blood revealed abnormality, the patient was kept long enough to permit the amount of urea and chlorides and the carbon dioxide-combining power of the blood to return to normal. In the majority of cases vitamins, usually two capsules of halibut liver oil and six tablets of brewers' yeast daily, were given routinely. In 19 cases cleansing enemas were given night and morning for two or three days before operation, and low residue or residue-free diets were employed throughout the preoperative period. In 15 of the 19 cases, 0.5 to 1.0 cc. of vaccine was given intraperitoneally in addition to the regular preparation of the colon. The prothrombin time (Quick test) was normal in instances in which it was obtained. Vitamin K was not given to the patients in this group. Fluids, usually a 5 per cent solution of dextrose in a 0.9 per cent solution of sodium chloride, were given intravenously to 24 of these 36 patients.

Group 3.—This group consisted of 7 patients who also were included in group 2. These patients are grouped separately because their preoperative preparation was as thorough as possible, and only 1 postoperative death occurred. All 7 of these patients were in worse condition on admission than the average patient of the total series. All were greatly emaciated, and 6 had marked nutritional edema of the ankles

and the abdomen. One had rather serious pyelonephritis, and another had mild mental changes, which together with his avitaminotic state and dermatitis suggested pellagra. The chemical findings in the blood were not more abnormal than is usual in this type of case, but in 2 cases the values for the proteins were less than 5 Gm. per hundred cubic centimeters of serum. Determinations of vitamin C in the plasma were made in only 3 of these cases; the values were below normal in all 3. However, in these 7 cases there was only 1 death, and that occurred on the seventeenth day after operation and was caused by peritonitis. Perhaps the fact that each of the patients was in even worse than usual condition on admission led to more painstaking preparation for operation. A postoperative mortality rate of only 14.2 per cent after repair of gastrojejunocolic fistula performed in one stage in 7 such cases is remarkable.

The average preoperative stay in the hospital for these 7 patients was slightly more than nine days. They all received daily at least 2,000 cc. of a 5 per cent solution of dextrose in a 0.9 per cent solution of sodium chloride intravenously. Two received transfusions of 500 cc. of citrated blood. In each case the colon was prepared in the usual way; that is, cleansing enemas were given morning and night for two or three days before operation. In addition, all patients received vaccine intraperitoneally, low residue diets and massive doses of added preparations of vitamins daily, the exact amounts depending on the patient's needs. The usual routine for the daily administration of such vitamins included: (1) 100 to 200 mg. of ascorbic acid orally or 100 mg. intravenously; (2) 100 to 150 mg. of nicotinic acid orally or 50 to 100 mg. intravenously; (3) 15 to 30 mg. of thiamine hydrochloride orally or 5 to 15 mg. intravenously; (4) 30 drops of percomorph liver oil; (5) some form of vitamin D (halibut or cod liver oil in bulk or capsules); (6) six to twelve tablets of brewers' yeast daily. These amounts were varied according to the patient's needs.

From study of groups 2 and 3 it is clear that no single therapeutic measure will cause significant lowering of the operative mortality rate. Each patient must be studied and treated individually. Hard and fast rules of preoperative management cannot be given, although a logical rationale of preoperative management is suggested by this study.

SURGICAL CONSIDERATIONS

If a procedure of one stage is contemplated for the repair of a gastrojejunocolic fistula, some such method of preoperative management would seem wise. Preliminary jejunostomy is recommended by some surgeons and in their experience has given good results. Scrimger⁸

8. Scrimger, F. A. C.: A Technic for the Management of Gastrojejunal Ulcers With or Without Gastrocolic or Jejunocolic Fistula, *Ann. Surg.* 104:594-600 (Oct.) 1936.

suggested a technic in which the edges of the gastric mucosa from the cuff of the anastomotic ulcer are sutured together over the fistula; a posterior Polya type of gastric resection is then carried out, utilizing portions of the jejunum distal to the fistula. In 5 cases reported, 1 death occurred. One patient in our series was subjected to preliminary jejunostomy but died thirteen days after the operation of perforation of a gastric ulcer and resulting peritonitis and uremia. Many other suggestions of technic have been advanced, occasioned no doubt by the high mortality rate attending the accepted types of repair. Allen³ has suggested resection of the colon, jejunum and stomach en masse by the Kerr aseptic technic of anastomosis for restoration of continuity of the gastrointestinal tract. Finsterer⁹ preferred to carry out the procedure in a single stage but recommended an operation in two stages if simple closure of the fistula could not be performed. Findlay¹⁰ recommended a multiple stage operation.

Perhaps one of the most encouraging suggestions is that of Pfeiffer,¹¹ who recommended preliminary loop colostomy in preparation for final repair of the fistula at a second stage. In this way the fecal current is diverted above the fistula, giving the inflammatory process at the site of the fistula time to heal and averting colonic contamination. The general condition of the patient can be improved greatly in this way in preparation for final repair of the fistula.

SUMMARY

A series of 49 cases in which patients were operated on at the Mayo Clinic from 1930 to 1939, inclusive, is reviewed from the standpoint of medical preoperative management. Of the 49 patients, 18 died after operation; the mortality rate was 36.7 per cent. Of 13 patients who received practically no preoperative preparation, 8 died; the mortality rate in this group, then, was 61.5 per cent. Of the remaining 36 patients, all of whom had fairly satisfactory preparation, 10 died—a mortality rate for this group of 27.7 per cent.

Only 1 of 7 patients, all of whom were in worse condition on admission than usual and who received careful and adequate preoperative treatment, died—a mortality rate of 14.2 per cent.

It is suggested the prohibitive mortality rate after reparative procedures performed in one stage for gastrojejunocolic fistula can be lowered materially by adequate preoperative management.

9. Finsterer, H.: Results of Repeated Operations upon the Stomach Especially for Gastrojejunal Ulcers, *Surg., Gynec. & Obst.* **68**:334-346 (Feb. 15) 1939.

10. Findlay, F. M.: Treatment of Gastrojejunocolic Fistula by Multiple Stage Operations, *Arch. Surg.* **32**:896-906 (May) 1936.

11. Pfeiffer, D. B., and Kent, E. M.: The Value of Preliminary Colostomy in the Correction of Gastrojejunocolic Fistula, *Ann. Surg.* **110**:659-668 (Oct.) 1939.

CONGENITAL DUODENAL OBSTRUCTION

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Acute intestinal obstruction is always such a serious illness that it demands prompt recognition and treatment to prevent a fatal termination. This is just as true when it occurs in infants as when it occurs in adults, with the further consideration that infants, being inarticulate, often are subjected to delay in diagnosis, and this results in their contributing more than their share to the high mortality rate.

When one is reminded that the first successful operation for the cure of duodenal obstruction in an infant was reported as recently as 1916,¹ there seems some justification for the past failures of those responsible for the medical care of infants to recognize the condition. That the point in pediatrics has been reached where the disease, whether acquired or congenital, is more promptly recognized is attested by the increasing number of cases reported. There has been an unjustifiable tendency to consider gastric and intestinal disorders of the baby as errors of digestion or nutrition, but this diagnostic complacency is rapidly being displaced by scientific and common sense observation on the part of physicians.

Congenital duodenal obstruction is not a common condition, but its frightful mortality rate gives it an importance among the diseases of infancy and childhood second to no other illness.

A brief résumé of the mechanical factors involved is a good background for the consideration of the symptoms and treatment. In the second and third month of fetal life,² the entire gastrointestinal tract is a simple rod of epithelium and mesoderm, with practically no lumen. The cephalic end dilates into a rudimentary stomach, the midportion

1. Ernst, N. P.: A Case of Congenital Atresia of the Duodenum Treated Successfully by Operation, *Brit. M. J.* 1:644 (May 6) 1916.

2. Callander, C. L.: *Surgical Anatomy*, Philadelphia, W. B. Saunders Company, 1933. Arey, L. B.: *Developmental Anatomy*, ed. 3, *ibid.*, 1934.

grows in length and assumes the form of superimposed coils, while the caudal extremity dilates slightly to become eventually the sigmoid flexure and the rectum. All of this embryonic tract lies on the left side of a shallow abdomen. The small bowel increases in length and projects itself, for lack of space, into and through the umbilicus into the cord so that, in reality, a hernia is created. For some reason unknown to those best qualified to state, the small bowel is retracted soon after and

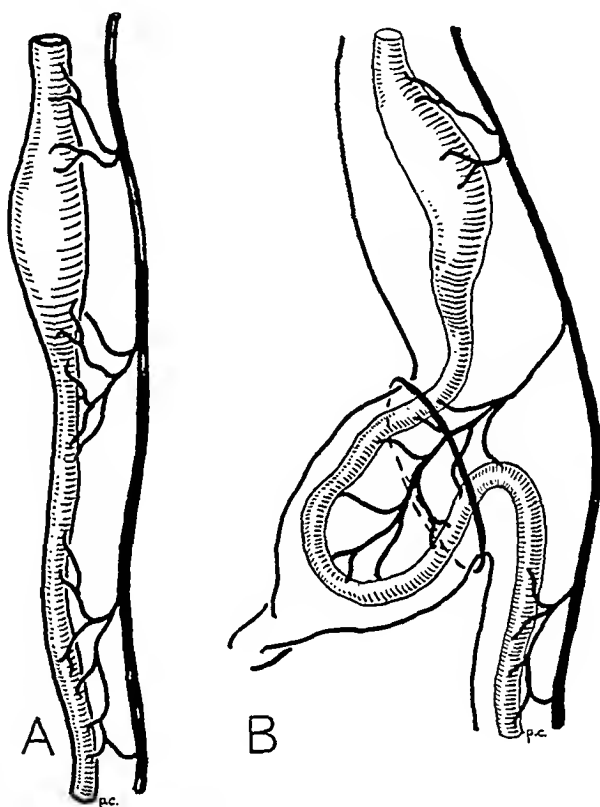


Fig. 1.—*A*, primitive gastrointestinal tract. *B*, elongation of the small intestine and its projection through the umbilical canal.

returns to the left side of the abdomen. An unyielding short mesentery is one explanation of the out and in mechanism. In the upper left quadrant of the abdomen, in the region of the spleen the large bowel joins with the small intestine and extends directly downward to become later the descending colon, sigmoid flexure and rectum. About the third month, the colon grows in length, pushing the cecum, which has been in the region of the spleen, over into the lower right quadrant of the abdomen, where it becomes firmly attached. This is known as the rota-

tion of the colon. In this movement, the leaf of the mesentery and the superior mesenteric artery are involved and apparently angulated to some extent. The colon continues to grow two of its fixed points, the

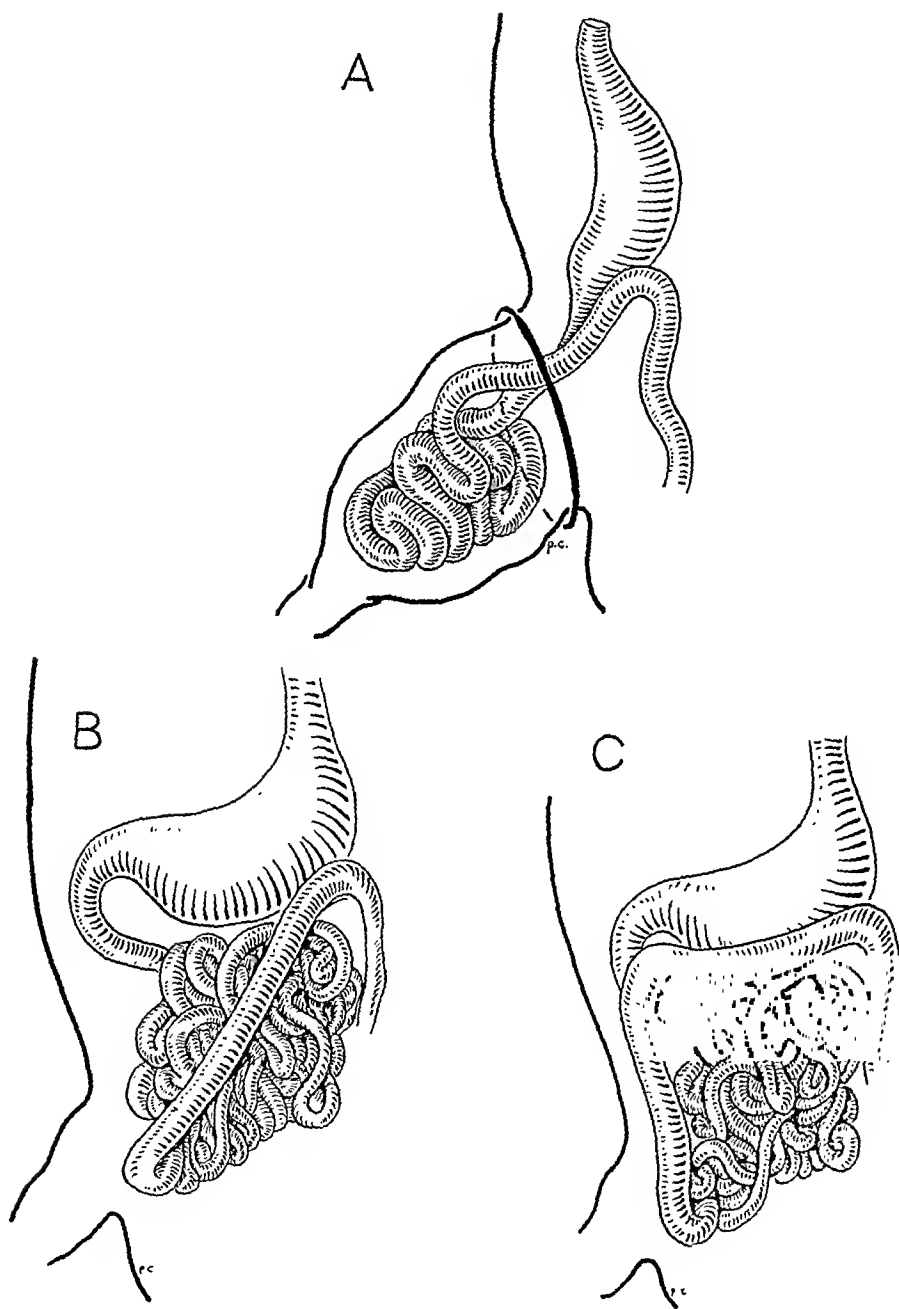


Fig. 2.—*A*, the small intestine greatly increases its length. *B*, the colon descends and rotates. *C*, the colon elongates to form the ascending and transverse colon.

lower right and the upper left quadrant of the abdomen, and the additional length goes into the space formerly occupied by the liver. The liver, which has been a relatively large organ up to this time, either

recedes beneath the ribs or actually diminishes in size. The portion of the large bowel filling this space becomes the ascending colon, hepatic flexure and transverse colon and covers the duodenum and proximal part of the jejunum. It is in this development and rotation that deviation from the normal manner results in angulation or compression of the duodenum. In all but 1 of every 20,000 cases the adjustment is perfect

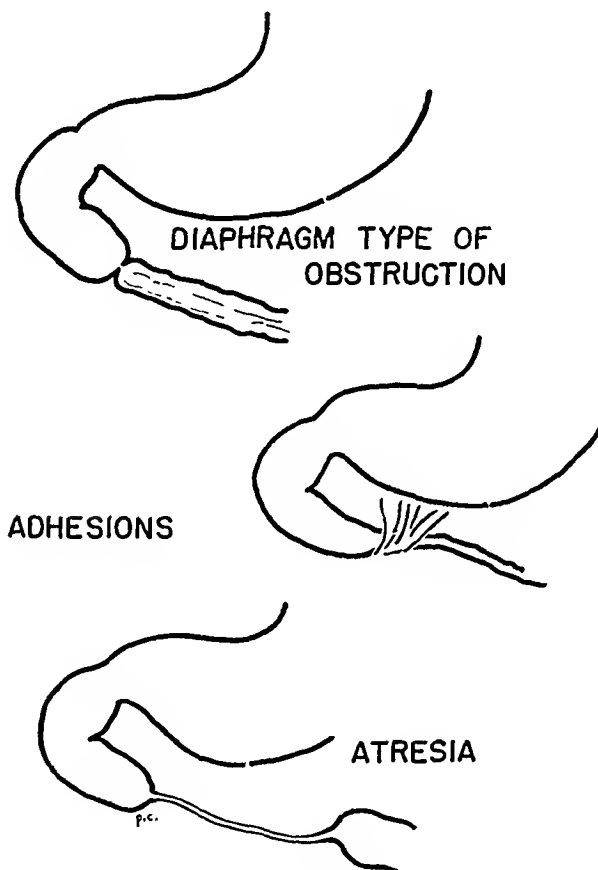


Fig. 3.—The types of duodenal obstruction.

and the function of the intestine is uninterrupted. The 1 case is that of duodenal obstruction.

Other forms of obstruction are recognized anatomically. An unusual type is one in which a diaphragm or septum develops within the duodenum; this is known as an intrinsic obstruction. The most common obstruction is the atresia or failure of the bowel to develop a lumen, leaving the intestine merely a stringlike continuation of the duodenum. This may be and often is multiple. It seems futile to seek an explana-

tion for these errors and defects in development; it is sufficient today to recognize their presence.

In most cases, the obstruction dates from birth, and, except in those rare ones in which an incomplete diaphragm is present in the duodenum, the onset of symptoms is prompt and continuous. Vomiting stands out as the most conspicuous and important symptom and is therefore entitled to the most careful consideration. It appears shortly after birth and continues until it is relieved by appropriate measures or until the patient

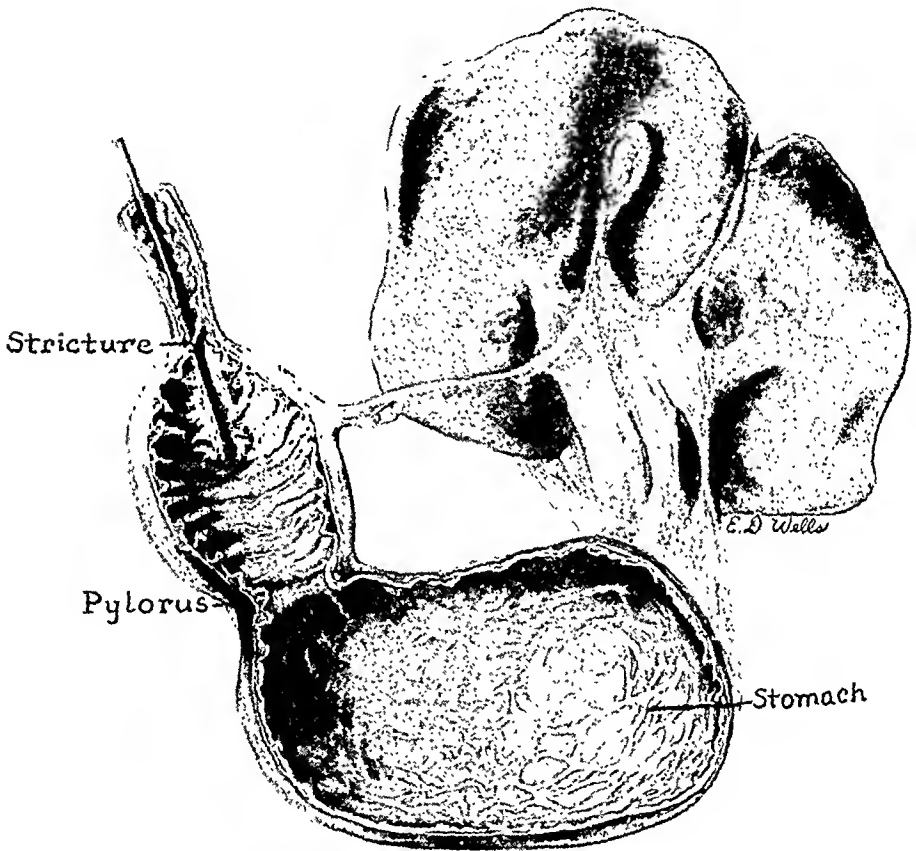


Fig. 4.—Specimen showing the intrinsic or diaphragmatic type of obstruction.

succumbs. It does not follow feeding as promptly as in pyloric stenosis, and in most instances bile and duodenal contents (readily recognizable by odor and color) are present.

The stomach may be dilated, and the physical examination should demonstrate this; the lower part of the abdomen, however, will be flat. There should be no hesitation in using a thin feeding of barium sulfate to outline the stomach and duodenum and thus localize the obstruction. As a rule, the stools consist chiefly of meconium.

It has been pointed out that if the lesion in the duodenum is proximal to the opening of the common bile duct, bile will not appear in the

vomit, and a picture identical with pyloric stenosis presents itself. A diagnosis of this condition in itself is no great commission of error if the obstruction is recognized and treated surgically when the differentiation is made at the time of operation. Suffice it to state that other symptoms of intestinal obstruction are present, and the recognition of the condition should not be insurmountable. Too much emphasis cannot be placed on the necessity of furnishing food and fluid to the dehydrated and starved victims of obstruction prior and subsequent to surgical measures.

In a reasonable search of the literature, we have found no accurate study made of comparative blood counts and blood analyses in these cases, but we have no doubt that they run parallel to those in the cases of adults. In the latter, moderate leukocytosis, decrease in chlorides and hypoproteinemia are the major changes. This should prove a valuable and interesting study.

It would seem that the urgency of these cases demands prompt diagnosis and surgical treatment. If there is any medical situation in which time is an element in the treatment, it must be acute intestinal obstruction in infants. In too many cases operation is postponed until no hope of a successful outcome can be entertained.

The diagnosis in most cases can be made on the basis of the short period after birth in which vomiting occurs, together with the persistence and type of the vomiting and the nature of the material ejected. Roentgen examination is of positive value and should be utilized more frequently. If the physician expects to delay and fortify the patient by intravenous injection of solutions or of blood, he is doomed to disappointment. The catalytic elements in the disease outweigh the constructive assistance furnished by parenterally injected solutions. McIntosh and Donovan³ observed:

Some of the authors writing on this subject have laid emphasis on the part played by volvulus in producing the symptoms of obstruction, while others have stressed the kinking and compression of the duodenum by congenital peritoneal bands and the constricting effect of other malformations of the mesentery. Our series includes examples of all of these types, and we wish to point out that preoperative differentiation among them is always difficult and often impossible.

The treatment is surgical. The intravenous injection of solutions prior to the operation is recommended, but temporizing with the hope of raising the resistance of the patient is not justified in the light of experience. Plasma is the logical substitute for blood and should be used freely.

There is no necessity for detailing the steps of the operation. The operator should always bear in mind that the patient offers a poor

3. McIntosh, R. R., and Donovan, E. J.: Disturbances of Rotation of the Intestinal Tract, *Am. J. Dis. Child.* **57**:116-166 (Jan.) 1939.

BASAL CELL CARCINOMA OF THE VULVA

REPORT OF FOUR CASES

JAMES M. WILSON, M.D.

DURHAM, N. C.

Considering all that has been written on the subject of carcinoma of the vulva, it is surprising to find that the basal cell type of tumor has received so little attention. This is particularly true when one considers its relatively benign nature in other parts of the body as compared with squamous carcinoma. That the tumor is uncommon is unquestioned; yet it occurs with sufficient frequency to warrant special consideration. The following study is based on the 4 cases reported here and on 23 additional cases collected from articles dealing with vulval carcinoma in general, found in the literature between 1916 and 1939. From this material an attempt is made to present data regarding the incidence, therapy and prognosis.

In order to clarify the term basal cell carcinoma the histopathologic picture must first be considered. Between the typical squamous carcinoma with its pearl-forming, large, clear cells and the classic basal cell tumor of Krompecher, there lies an intermediate group, referred to as "transitional cell" carcinoma, or *épithéliome intermédiaire*.¹ Within this group one sees variation all the way from one extreme to the other; it is the middle portion of the curve of expected biologic mutation of such a pleomorphic structure as the epidermis. For the sake of this discussion I have included the transitional cell carcinoma with the basal cell, largely because of the similar rarity of metastasis which it manifests; its greater radioresistance as compared with the typical basal cell tumor must be remembered, however. Not included in this discussion is the mixed basal and squamous cell carcinoma; because of its definite metastatic tendencies it must for practical purposes be considered a squamous cell carcinoma. It does occur on the vulva. Schreiner and Wehr² men-

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1. Darier, J., and Ferrand, M.: *Forme métatypique du cancer malpighien de la peau et des orifices muqueux*, Ann. de dermat. et syph. 3:385-406, 1922.

2. Schreiner, K., and Wehr, W. H.: *Cancer of Vulva, with Report of One Hundred and Eighteen Cases*, Surg., Gynec. & Obst. 58:1021-1026 (June) 1934.

formed 1 case, without details. Petit-Dutaillis³ recorded 2, 1 of which was not followed; in the other the tumor recurred six months after a radical vulvectomy. It is, then, with this preliminary understanding that the following study is undertaken.

THE PRESENT STUDY

In 60,000 surgical specimens that have been examined in the department of pathology in the Duke hospital, carcinoma of the vulva has been diagnosed 32 times. Of the 32 tumors, 4 were of the basal cell type, an incidence of 12.5 per cent. The clinical data on cases 1 and 2 are available through the courtesy of the physicians who submitted the surgical material for study. Case 1 was subsequently observed here, when the patient was referred for roentgen therapy.

CASE 1. Mrs. C. M., white, 58 years old, had passed the menopause nine years prior to examination. A small painless nodule had been present "at the edge of the vagina," in relation to the vulvovaginal gland, and had been slowly growing over a period of seventeen years. In the six months preceding operation it had rapidly increased in size, becoming ulcerated and painful. The condition of the inguinal nodes at that time is not known. Local excision with a wide margin was done. Seventeen months later she was referred to the Duke Hospital for treatment of a recurrence at the site of the original lesion. Over an area approximately 3 cm. in diameter she received 392 milligram hours of interstitial radium and 1,500 r of high voltage roentgen radiation over the perineum and the inguinal regions (formula: 170 kilovolts; 4 milliamperes; 40 cm.; filtration, 0.5 mm. each of copper and aluminum). She did not complete the course recommended. She was seen again nineteen months later, when no evidence of tumor could be demonstrated by physical examination, but four years after operation she is said to have died of local metastases to the bladder and rectum.

The surgical specimen (fig. 1A) was an irregular mass of tissue measuring 8 by 6 by 6 cm. and covered on one surface by a 3 cm. fragment of skin. Centrally there was a firm white tumor mass measuring 4 by 4 by 5 cm. and surrounded by necrotic material containing small cysts.

Microscopic interpretation of the tumor was difficult. The large firm mass was obviously a fibroma. The necrotic cystic material appeared to be the vulvovaginal gland diffusely involved by an epithelial tumor, the larger "cysts" being dilated ducts lined with the neoplasm, some of them measuring as much as 0.5 cm. in diameter. In most of these the tumor seemed rather well circumscribed, but in many others it tended to invade the surrounding supporting stroma (fig. 1B). In still other areas large and small masses of the carcinoma were seen apparently in no relation to any glandular structure, diffusely invading the surrounding tissue, even the superficial portion of the fibroma. Both types of growth showed more or less honeycombing, such as is seen in the cystic type of basal cell carcinoma. A small amount of brown pigment was scattered throughout, and in the superficial areas there was considerable evidence of acute and chronic inflammation.

3. Petit-Dutaillis, P.: *Considérations sur le début, l'évolution et le traitement des épithéliomes primitifs de la vulve, d'après dix-sept cas observés et traités*, Gynécologie 31:65-81 (Feb.) 1932.

Histologically the tumor cells were rather closely packed, the outlines of the palely acidophilic cytoplasm being obscured. The nuclei were elongated and fairly dense and showed rather numerous mitoses. Nothing resembling pearl formation was noted. The tumor was classed as a transitional cell carcinoma of the basal cell type.

As to the origin of the tumor one can only guess. Certainly in some areas origin in the vulvovaginal gland was suggested, but its advanced state precluded

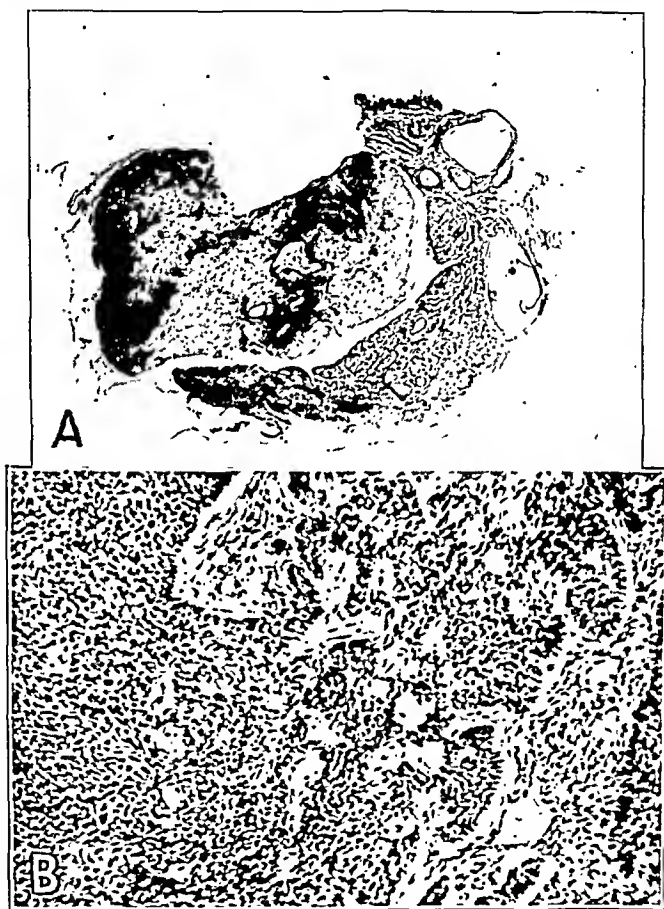


Fig. 1 (case 1).—*A*, lantern slide section, natural size, of the entire gross specimen. Note the edge of the skin (above); the fibroma (to the left), and the tumor of Bartholin's gland (to the right). Hematoxylin and eosin. *B*, invasion of the stroma where the large mass of cells breaks through the basement membrane of the gland. The growth is of the transitional cell type. Hematoxylin and eosin; $\times 127$.

anything but speculation. Of particular interest, however, is the long-standing fibroma, a possible source of chronic irritation.

CASE 2.—Mrs. G. L., 47 years old, white, had in the past received intensive antisyphilitic therapy over a long period. A small growth had been present "in the axilla" for three years. This had been "sore" and had caused extreme pain, but only in the three months preceding operation had it begun to bleed and cause severe discomfort. Examination showed an indurated ulcer 3 cm. in diameter on the lower margin of the right labium majus. The right inguinal glands were tender but only slightly enlarged.

At the time of the biopsy extensive electrocauterization was done over the ulcerated area, followed by (1) administration of 4,000 r in twenty-two days through a vaginal, an anterior and a posterior port (200 kilovolts; 20 milliamperes; filtration, 0.5 mm. of copper and 1 mm. of aluminum; 50 cm. distance) and (2) 2,000 r over the right inguinal region in twenty-eight days, the formula being the same

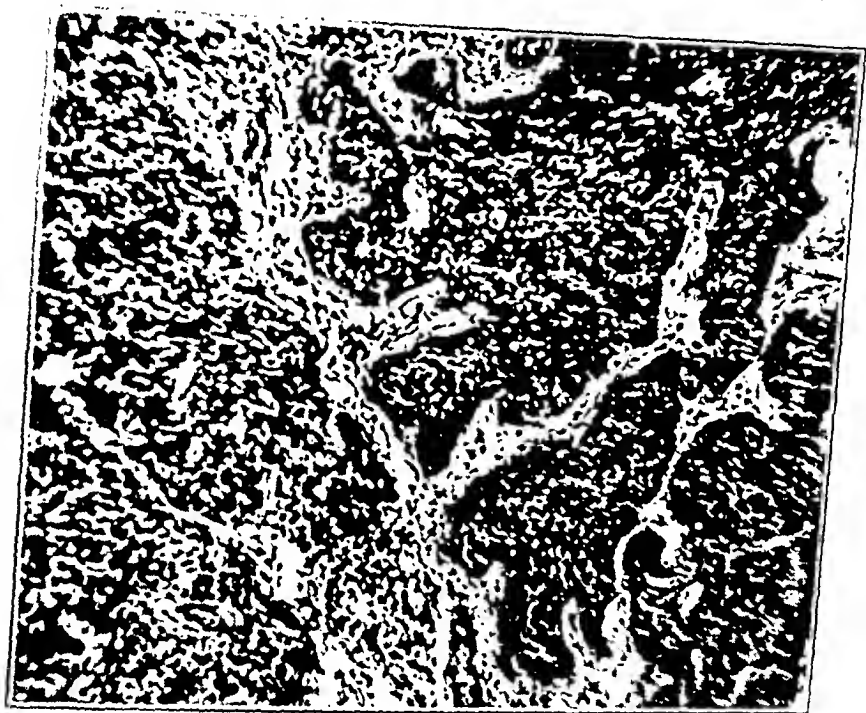


Fig. 2 (case 2).—Field showing a typical basal cell carcinoma. Hematoxylin and eosin; $\times 127$.

except that a Thoracuss (copper, tin and aluminum) filter was substituted. However, there was early recurrence, and the patient died fifteen months after the first operation.

Histologically (fig. 2) the biopsy specimen showed ulceration of the epithelium with infiltration of the subcutis by masses of typical basal cells. The nuclei were oval, dark and sharply outlined and showed numerous mitoses. The depth of penetration into the deeper tissue could not be estimated.

CASE 3.—Mrs. E. R., 71 years old, white, had borne five children, all of whom were living. She had passed the menopause twenty-six years previously. A small itching pimple had been present on the anterior left labium majus for nine months, slowly increasing in size. It was slightly indurated, slightly elevated and grossly

ulcerated. The inguinal nodes were not enlarged. The diagnosis on biopsy was basal cell carcinoma, and a simple vulvectomy was done. Twenty-two months later the patient was in good health; there was no sign of local recurrence and no enlargement of the inguinal nodes.

On section the tumor was found to be superficial, measuring 2 cm. in diameter and from 1 to 3 mm. in thickness. Histologically (fig. 3) the cells were of the same type as those seen in case 1, even showing the same honeycombed arrangement. This growth, too, was designated as a transitional cell carcinoma of the basal cell type.

CASE 4.—Mrs. T. F., 59 years old, white, had borne six children, five of whom were living. She had passed the menopause nine years previously. She was first



Fig. 3 (case 3).—Note the similarity of the cellular morphologic structure to that in figure 1 B. Hematoxylin and eosin; $\times 127$.

seen in 1932, complaining of pruritus of one year's duration. A mild vaginal discharge was present. Biopsy of the cervix showed chronic cervicitis, which cleared up rapidly with simple douches. Six months later, because of persistence of the pruritus 160 milliampere minutes of roentgen therapy was given over the perineum. In 1935, because of continued discomfort, a partial vulvectomy was done, the left labium majus being removed. Eighteen months later she was found to have mild intertrigo in the left inguinal fold with continued pruritus in the left vulval region. From this area in 1939 a tiny superficial papillary nodule was removed under the impression that it was an epidermoid (sebaceous) cyst. Although it proved to be carcinoma, no further surgical or roentgen treatment was instituted, and there has been no recurrence in twenty months.

The gross surgical specimen measured but 2 mm. in its greatest diameter, and on serial section the tumor was thought to have been completely removed with

to a definite margin. Histologically (fig. 4) it presented a typical picture of cystic basal cell carcinoma, the nuclei being oval and dark and presenting numerous mitoses.

In only 17 of the 23 collected cases were sufficient clinical data for study recorded; these are listed in detail in table 1, together with the 4 cases reported here. One of the remaining 6 was mentioned by Temesváry⁴ as being reported by Prytek; no reference was given. Thorough search of the literature has revealed no more than a mere mention of such a case in an article dealing solely with the histologic character of this



Fig. 4 (case 4).—Typical cystic basal cell carcinoma. Hematoxylin and eosin; $\times 127$.

type of tumors⁵; no clinical details were given. Another case was mentioned by Mosto and Radice,⁶ again with no clinical details. The remain-

4. Temesváry, N.: Ueber ein multiples Krompecher'sches Karzinom der Vulva, mit ausgedehnter Elephantiasis, Zentralbl. f. Gynäk. 50:1575-1582 (June 12) 1926.

5. Prytek: Ueber die Plasmazellen bei Epitheliomen der Haut, Arch. f. Dermat. u. Syph. 120:611-620, 1914.

6. Mosto, D., and Radice, J. C.: Tumores de vulva, benignos y malignos: Histopatología y consideraciones sobre 34 casos de tumores primitivos, Rev. med. y cien. afines 1:33-51 (Nov. 30) 1939.

ing 4 were found among the 9 cases recorded by Göbel and Hamann;⁷ no detailed information was given, and it is presumed that the patients died, whether or not of carcinomatosis is not known.

ANALYSIS AND COMMENT

Since each case or series of cases is lacking in certain details and since the total number is small, the following statistical studies are not entirely satisfactory. They are to be considered only as approximations, and in each analysis the possibility of misleading conclusions should be considered.

In an attempt to ascertain the incidence of the basal cell type of lesion the 5 cases of Prytek, Temesváry, Leigheb,⁸ Claiborn and Holsinger⁹ and Hinselmann¹⁰ must be omitted; they are isolated, not being recorded in relation to a whole series. Table 2 shows the remaining cases, including those reported by Delporte and Cahen,¹¹ Eichenberg,¹² den Hoed¹³ and Nuytten and Garraud.¹⁴ It also includes by way of comparison the series of Schreiner and Wehr² and of Rentschler¹⁵ and Tausch;¹⁶ several other such series, which are not included, were found in the literature. The close approximation of the first 4 as compared with the others is startling, and, since it does not seem possible that the element of individual histologic interpretation could account for so wide a divergence, I am at a loss for a suitable explanation.

Regarding etiologic factors, I find that chronic irritation was known to have been present for a considerable time in 3 of my 4 cases; in none,

7. Göbel, A., and Hamann, A.: *Zur Klinik und Therapie der Karzinome am äusseren Genitale*, Zentralbl. f. Gynäk. **61**:1394-1419 (June 12) 1937.

8. Leigheb, V.: *Epitelioma basocellulare superficiale della vulva dissimulato da fatti eczematoidi*, Gior. ital. di dermat. e sif. **69**:1566-1572 (Dec.) 1928; cited by Claiborn and Holsinger.⁹

9. Claiborn, L. N., and Holsinger, H. B.: *Basal Cell Carcinoma of Vulva*, Surg., Gynec. & Obst. **54**:836-838 (May) 1932.

10. Hinselmann, H.: *Ein sehr kleines Vulvakarzinom*, Ztschr. f. Geburtsh. u. Gynäk. **103**:15-21, 1932.

11. Delporte, F., and Cahen, J.: *Contribution à l'étude du traitement radio-chirurgical des épithéliomas de la vulve et de l'urètre*, J. de chir. **41**:861-891 (June) 1933.

12. Eichenberg, H. E.: *Beitrag zur Pathologie des Vulvakarzinoms*, Ztschr. f. Geburtsh. u. Gynäk. **108**:276-302, 1934.

13. den Hoed, D.: *Results Obtained in the Treatment of Malignant Tumors of the Vagina, Vulva and Urethra*, Acta radiol. **17**:569-578, 1936.

14. Nuytten, J., and Garraud, R.: *Valeur de la curiethérapie dans le traitement du cancer de la vulve*, Gynec. et obst. **36**:508 (Dec.) 1937.

15. Rentschler, C. B.: *Primary Epithelioma of Vulva: Analysis of Seventy-One Cases*, Ann. Surg. **89**:709-730 (May) 1929.

16. Tausch, M.: *Beitrag zur Klinik und Statistik des Vulvakarzinoms*, Monatsschr. f. Geburtsh. u. Gynäk. **89**:402-419 (Dec.) 1931.

Table 1. Summary of Cases

Date and Author	Author's Pa- Case No.	Age	Etiologic Factors	Location	Para- tion	Size	Regional Notes	Treatment	Results	Date of Case	Comments	Photomicro- graphs sug- gest basal cell
Wilson	1	53	Fibroma of labium for 17 years	In Bartholin's gland?	6 mo.	3-6 cm.	?	Local excision; radi- cal vulvectomy	Died	1927	Transverse	Basal cell
Wilson	2	47	?	Right labium majus	3 yr.	3 cm.	Slightly enlarged bilaterally	Radical vulvectomy; high voltage irradiation	Died	1928	Transverse	Basal cell
Wilson	3	71	Obesity; intertrigo; no pruritus	Left labium majus	9 mo.	Diameter 2 cm.; thickness 3 mm.	Not enlarged	Simple vulvectomy	Living; no recurrence	1929	Transverse	Basal cell
Wilson	4	59	Pruritus for 7 years	Left labial region; labiectomy 4 years before	?	2 mm. diameter	Not enlarged	Local excision	Living; no recurrence	1929	Basal cell	Basal cell
1926 Temesváry	1	53	Recurrent erysipelas for 10 months	Multiple, on labia majora	10 mo.	Scattered nodules averaging 0.5 cm.	?	?	Died	3 mo.	Cellular culture	Basal cell
1927 Leigheb ⁸	1	68	Pruritus for 2 years; leukoplakia	?	?	?	Enlarged bilaterally, negative on pathologic examination	Radical vulvectomy	Died	7 days (post-operative)	Broncho-pneumonia	Basal cell
1932 Claborn and Holsinger ⁹	1	69	Pruritus for 34 years	Left labium majus	?	3×2.5×0.6 cm.	Not enlarged	Local excision	Living; no recurrence	6 mo.	Basal cell	Basal cell
1932 Hinselmann ¹⁰	1	54	Pruritus for 7 years	Left labium majus	12 mo.	1.3×0.7×0.2 cm.	Not enlarged	Left labiectomy	?	?	Basal cell	Photomicrographs suggest basal cell
1933 Delaporte and Cohen ¹¹	10	40	?	On right from meatus to fourchet and into vagina	?	Very large; see "location"	Bilaterally enlarged; right positive on pathologic examination	Radium; radical vulvectomy 14 mo. later	Died	17 mo.	Carcinoma	Basal cell
1933 Delaporte and Cohen ¹¹	22	45	?	Periurethral extending into vagin 2 cm.	?	See "location"	Not enlarged	Radium, 8,125 mg. hours	Living; urinary incontinence	7 yr.	Basal cell	Basal cell

	24	80	?		?	See "Joention"	Not enlarged	Radium, 4,262 mg. hours	Died	8 mo.	Cardiorenal disease	0	Basal cell
1923 Delporte and Cabon ¹¹													
1934 Eichenberg ¹²	1	72	?	Periurethral extending into vagina 5 cm.	1 yr.	"A small hand"	?	Radium, amount unknown	Recur- rence in 8 months	?	Basal cell
1934 Eichenberg ¹²	2	66	Pruritus for 10 years	Left labium minus	2 yr.	"A small hand," extended into vagina	Implied negative to pathology examination at autopsy	"Exelsion"	Died	Death immediately postoperative	Pulmonary embolus	"No evidence of tumor"	Basal cell
1936 dea Hood ¹³	1	?	?	?	?	?	?	?	Living; no recurrence	5 yr.	Basal cell
1937 Nuytten and Garraud ¹⁴	5	66	Pruritus; duration ?	On left from clitoris to anus	4 mo.	See "Joention"	Bilaterally enlarged	Radium, amount unknown	Died	5 mo.	?	0	Basal cell
1937 Nuytten and Garraud ¹⁴	16	10	?	Left labium and cervix	?	?	Slightly enlarged on left	Radium and high voltage irradiation; amount not clear	Vulval recurrence 8 months; extension of cervical lesion	?	"Malignant epithelioma with tendency to basal cell type"
1937 Göbel and Hamann	12	77	?	Right labium minus	?	?	Not enlarged	Operation; radium, amount unknown	Died	14 mo.	Broneho- pneumonitis dense of carcinoma	No cvi- dence of carcinoma	Basal cell
1937 Göbel and Hamann	3	62	?	Mentus	2 yr.	?	Not enlarged	Electro- coagulation	Recur- rence in 13 mo.; therapy repeated; living	14 yr.	Basal cell
1937 Göbel and Hamann	5	70	?	Left labium majus	2 mo.	?	Enlarged on left	Electro- coagulation	Living; no recurrence	13 yr.	Basal cell
1937 Göbel and Hamann	6	73	?	Clitoris	?	?	Enlarged bilaterally	Electro- coagulation	Living; no recurrence	10 yr.	Basal cell
1937 Göbel and Hamann	9	51	?	Clitoris	3 mo.	?	Enlarged on left	Tumor with radium needles, nodes with roentgen therapy; amounts not stated	Living; no recurrence	5 yr.	Basal cell

* See original publication.

† Three other cases of "epithelioma malignum du type intermédiaire" are listed (cases 4, 6 and 11); as it is not clear what this term means, they are not included in table 1. All 3 patients were treated with radium. In cases 4 and 11, in which the tumors occurred on the labia, the patients died the second day after necrosis. In the third (case 6), a case of tumor of the urethral meatus, the patient was living five years after treatment (30.03 millicuries destroyed) without recurrence.

however, was there leukoplakia. Of the 17 collected cases, in only 6 were etiologic factors suggested and in only 1 was leukoplakia mentioned. This is especially interesting when one considers that basal cell tumors almost never arise from leukoplakia of mucous membranes (e. g., those of the mouth), their most common origin being from the waxy hyperkeratoses of the face.

Table 3, which shows the site of origin, is self explanatory.

TABLE 2.—Incidence

Series	Total Number of Vulval Carcinomas	Number of Basal Cell Carcinomas	Percentage of Basal Cell Carcinomas	Number of Mixed Basal and Squamous Cell Carcinomas	Percentage of Mixed Basal and Squamous Cell Carcinomas
D. & H. Spitz.....	52	4	12.5	0	0
DeMeester and Garbutt.....	25	3	12.0	0	0
Mayhew and Garrard.....	17	2	11.8	0	0
Gillette and Hamman.....	61	9	14.7	0	0
K. & L. Spitz.....	114	2	1.7	0	0
den Hartog.....	41	1	2.4	0	0
Martin and Hodge.....	21	1	4.7	0	0
Schlesinger and Weber.....	118	0	0	1	0.8
Reuter.....	71	0	0	0	0
Tamplin.....	54	0	0	0	0

TABLE 3.—Site of Predilection

Labia Majora	Labia Minora	Meatus	Clitoris	Bartholin's Gland
11	2	3	2	1 (?)

TABLE 4.—Condition of Inguinal Nodes

Not Enlarged	Status Unknown	Enlarged			
		Unilateral	Bilateral	Proved Positive	Proved Negative
8	4	3	3	1	2

There is no essential difference in this respect from squamous carcinoma. I may note here that both the tumors arising on the clitoris and 2 of the 3 which took origin at the meatus showed no recurrence in periods ranging from five to fourteen years.

The status of the inguinal nodes is shown in table 4.

In only 3 of 9 cases in which enlargement was present was histologic examination done. In the single case in which the inguinal nodes were involved the original lesion was very large, and the possibility of direct extension rather than lymphatic metastasis must be considered. It should be noted also that 3 patients with enlarged nodes lived beyond the five year limit, only 1 of whom received irradiation over the nodes.

Table 5, showing the mortality rate, is the most important and least satisfactory of all. For the sake of accuracy I must include the 4 cases of Göbel and Hamann not shown in table 1, making a total of 25; these authors listed in detail only their autopsies and five year cures, so that the remainder of the patients must be presumed to be dead.

The statistical picture is not bright, the five year salvage being only 24 per cent. Although 20 per cent of the patients died of causes other than carcinoma, 2 of the 5 deaths were postoperative and are therefore useless as follow-ups. And, while only 12 per cent of the patients are known to have died of carcinoma, 2 of the 3 listed under "status questionable" showed recurrence when last seen. To these must be added the 4 patients of Göbel and Hamann, making a total of at least 9, or 36 per cent, to be considered as having died of cancer.

The foregoing figures, however, must be interpreted in the light of certain other facts. Owing to the advanced age of most of the patients (average 60 years), the expected death rate from other causes will cut

TABLE 5.—*Mortality Statistics*

	Status Question- able	Died of Carcinoma	Presumed Dead *	Died of Other Causes	Died; Cause Unknown	Living Less than Five Years	Living More than Five Years
Number.....	3	3	4	5	1	3	6
Per cent.....	12	12	16	20	4	12	24

* The 4 patients of Göbel and Hamann, previously mentioned.

down the possible five year salvage. In addition, the two factors of duration and size of the tumor have a definite bearing on the outlook. The known biologic characteristics of slow growth and infrequency of metastasis constitute an incontrovertible fundament for a fair prognosis. This is borne out by the series of Göbel and Hamann, which contains the largest number of basal cell tumors; analysis of their figures shows a five year salvage of 44 per cent, obtained, as Taussig¹⁷ has shown, with what would constitute woefully inadequate therapy in the case of squamous carcinoma.

Regarding the type of treatment indicated, only generalization can be made. I do not feel that the radical Basset type of operation advocated by Taussig is indicated in cases of basal cell carcinoma. On the other hand, the figures just cited should give the surgeon a healthy respect for the tumor and prevent his judgment from being lulled into a false sense of security by the biopsy report of a basal cell lesion; vulval carcinoma is notoriously treacherous. Surgical intervention, irradiation and electrocautery have all given good results, the last

17. Taussig, F. J., in Pack, G. T., and Livingston, E. M.: Treatment of Carcinoma and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940, vol. 2, p. 1789.

especially in the hands of the German school. Common sense requires that in each case one take into consideration the size, duration and accessibility of the lesion; the operative risk, and the skill of the surgeon. With the possibility of good plastic repair, I personally advocate wide excision by the scalpel. When the meatus is involved or when the growth has extended to any degree into the vagina, radium or roentgen therapy seems logical. Each case must be individualized.

SUMMARY

Four cases of primary basal cell carcinoma of the vulva are reported, together with 23 cases collected from the literature.

The general incidence varies considerably, being 12 per cent of 32 primary vulval carcinomas at the Duke Hospital.

The death rate from the tumor itself is estimated to be at least 36 per cent in the entire series.

It is felt that, while the condition is serious, it carries a better prognostic import than does the squamous cell lesion.

I do not believe that the radical Basset operation is indicated. It is my opinion that when possible wide local excision should be done.

Attention is called to the transitional cell type of carcinoma, which, like the basal cell carcinoma, metastasizes infrequently.

SPINOTHALAMIC TRACTOTOMY² IN THE MEDULLA OBLONGATA

AN OPERATION FOR THE RELIEF OF INTRACTABLE NEURALGIAS
OF THE OCCIPUT, NECK AND SHOULDER

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Not infrequently the neurosurgeon is confronted by a case of intractable pain distributed so high over the shoulder and neck that it cannot be interrupted by cordotomy, no matter how high the spinothalamic tract is sectioned in the cervical portion of the spine. Pain of this type is most often due to neuralgia arising in an amputation stump of the upper part of the arm or shoulder or caused by avulsion or carcinomatous infiltration of the brachial plexus or to one of the rare unexplained neuralgias which may follow an operative incision or a penetrating wound of the neck or upper part of the back. As is well known, such conditions have been most difficult to relieve, even with extensive resection of the posterior cervical sensory roots and the consequent sacrifice of a useful arm.

It has been observed clinically in patients with thrombosis of the posterior inferior cerebellar artery (fig. 1) that loss of pain and temperature sensation usually involves the entire opposite side of the body, as well as the ipsilateral side of the face (Wechsler¹). The reason for this is that the descending trigeminal root (uncrossed) and the spinothalamic tract (crossed) lie side by side in the lateral part of the medulla, between the inferior cerebellar peduncle (restiform body) and the inferior olive. Both are included in the area of thrombosis. The descending trigeminal tract lies just dorsal to the vagal rootlets which emerge at this point, whereas the spinothalamic tract lies just ventral to and between the emerging vagal rootlets and the olive (figs. 2 and 3). These figures also show that the tract is relatively accessible to surgical division at this level. As in the spinal cord, only a thin layer of fibers of Gowers' indirect spinocerebellar tract lies peripheral to it. The rubrospinal tract and the descending root of the fifth cranial nerve are situated dorsally and the inferior olivary nucleus ventrally. Medially

From the Neurosurgical Service of the Massachusetts General Hospital.

1. Wechsler, I. S.: *A Text-Book of Clinical Neurology*, ed. 2, Philadelphia, W. B. Saunders Company, 1933, p. 368.

in the reticular substance lie the nucleus ambiguus (voluntary motor nucleus of the vagus), the dorsal accessory olivary nucleus and the descending sympathetic axons. The olivocerebellar fibers traverse this area. From all that is known, no appreciable disability should be produced if some of these fibers or even some of the substance of the dorsal, or inferior, olive should be cut. This is likewise true of injury to Gowers' tract, which is severed at every spinal section of the spinothalamic tract, and also of injury to the rubrospinal tract. The important pyramidal tract lies ventral to the inferior olive, where it is well protected from injury considering its vulnerable position in the spinal cord.



Fig. 1.—Infarction of medulla after thrombosis of the posterior inferior cerebellar artery on the right side. (From Wechsler's "Text-Book of Clinical Neurology,"¹ by permission of W. B. Saunders Company.)

The anatomic position of the spinothalamic tract at different levels is best illustrated in Walker's² study of its degenerated axons (fig. 4). Above the restiform body (fig. 4*B*) the tract occupies a much deeper position beneath the cerebellar peduncles, but it again comes close to the surface of the brain stem in the mesencephalon, at the point where the trochlear nerve roots are given off (fig. 4*A*). This is at the level

2. Walker, A. E.: The Spinothalamic Tract in Man, *Arch. Neurol. & Psychiat.* 43:284-298 (Feb.) 1940.

of the tentorium, and the tract has been interrupted here by Dogliotti.³ Exposure of the brain stem at the incisura of the tentorium is deep. Dogliotti's 3 surviving patients were freed of pain but complained of "unpleasant and undetermined feelings (paresthesias) diffused to the half of the body opposite to the side operated on." To the surgeon with experience in operations in the posterior fossa and especially in the

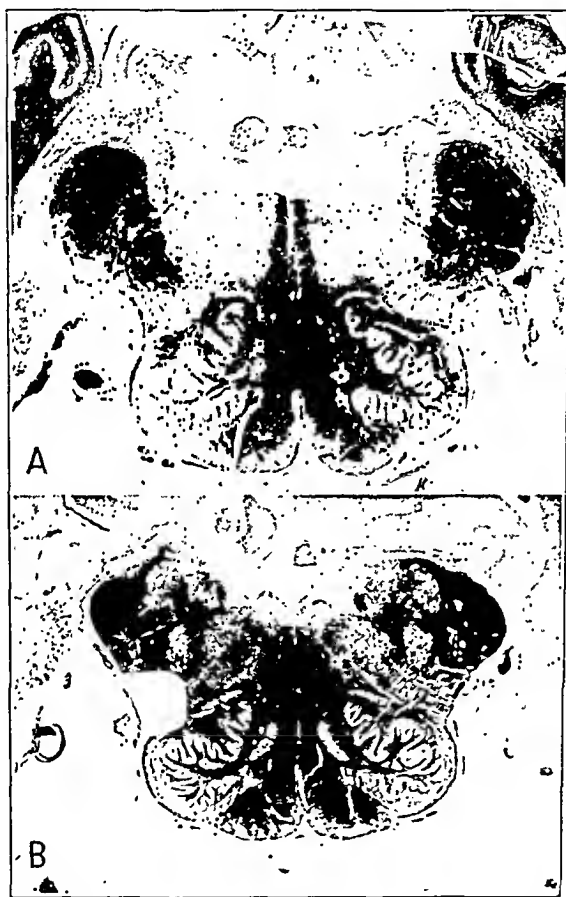


Fig. 2.—*A*, cross section of the medulla oblongata at the point of emergence of the ninth and tenth cranial roots. On the left side the posterior inferior cerebellar and vertebral arteries are shown close to the side of the medulla, as was the situation in the case described here. *B*, the medulla just below the last vagal rootlet, the level at which the spinothalamic tract was sectioned. The area cut across is illustrated in white. In this section the vertebral artery is situated more laterally, rather than pressed against the side of the inferior olive, as is usually the case.

3. Dogliotti, M.: First Surgical Sections, in Man, of the Lemniscus Lateralis (Pain-Temperature Path) at the Brain Stem, for the Treatment of Diffused Rebellious Pain, *Anesth. & Analg.* 17:143-145, 1938.

trigeminal tractotomy devised by Sjöqvist,⁴ a medullary section of the spinothalamic tract between the levels illustrated in figures 4 C and 4 D would seem to be a more practical procedure.

This operation was first performed by Schwartz, of St. Louis, and the case was reported by Schwartz and O'Leary⁵ at the meeting of the Society of Neurological Surgeons in April 1940. Unfortunately, their patient, who suffered from advanced malignant disease, failed to survive the operation for more than a few days, but it was possible to make a fairly satisfactory postoperative neurologic examination. This showed the expected high level of analgesia and thermoanesthesia, with no visible impairment of other important tracts. In this article there is a brief added note about a second patient in whom Dr. Schwartz cut the left spinothalamic tract at the level of the inferior olive. This fully

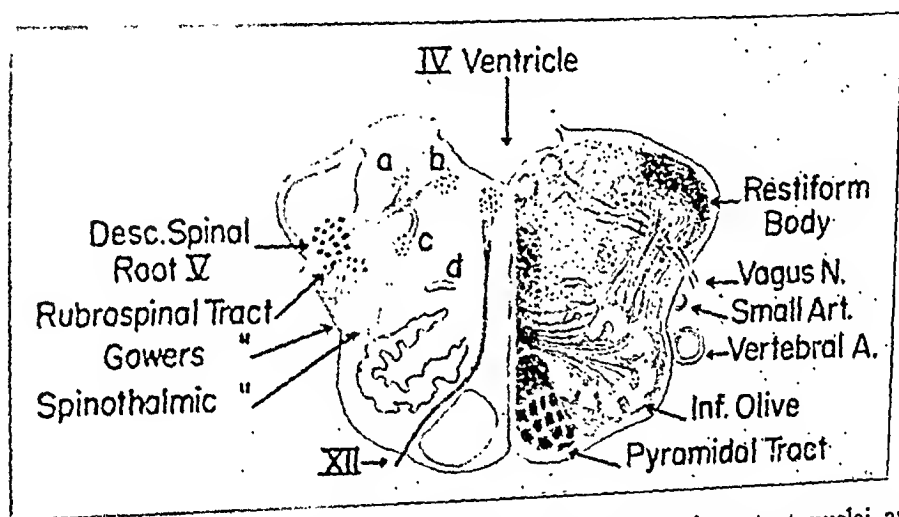


Fig. 3.—Drawing to illustrate the position of the more important nuclei and fiber tracts in the medulla. Note (a) the tractus solitarius; (b) the dorsal motor nucleus of the vagus nerve (autonomic); (c) the nucleus ambiguus (voluntary motor nucleus), and (d) the dorsal accessory olivary nucleus.

eliminated pain in the chest, shoulder and axilla caused by metastases from carcinoma of the breast. No complications from injury to neighboring structures were observed.

The case to be reported corroborates the observations of Schwartz and O'Leary, except that an otherwise perfect result was complicated by cerebellar ataxia. This complication, as will be pointed out later,

4. Sjöqvist, O.: Studies on Pain Conduction in the Trigeminal Nerve: A Contribution to the Surgical Treatment of Facial Pain, *Acta psychiat. et neurol.* 1938, supp. 17, pp. 1-139.

5. Schwartz, H. G., and O'Leary, J. L.: Section of the Spinothalamic Tract in the Medulla with Observations on the Pathway for Pain, *Surgery* 9:183-193, 1941.

can probably be avoided, and the operation then will constitute a brilliant application of knowledge gained from neuroanatomic investigation to the neurosurgical treatment of pain. The opportunities for relieving a number of hitherto intractable painful syndromes opened up by a practical method of sectioning the spinothalamic tract in the brain stem are so far reaching that further experience with this method is of con-

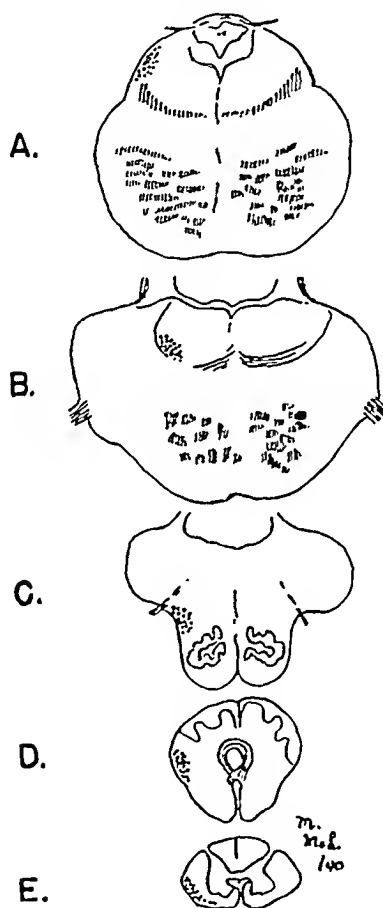


Fig. 4.—The position of the spinothalamic tract at various levels of the brain stem and spinal cord, according to Walker.² *A*, upper part of pons; *B*, lower part of pons; *C*, medulla oblongata at the level of the olive; *D*, lower part of the medulla; *E*, second cervical segment of the spinal cord.

siderable importance. This is the reason for the following detailed account of a young woman in good general condition who has recovered from the operation and has been freed of intractable neuralgia of the neck, shoulder, arm and upper part of the chest of three years' duration. It is unnecessary to give a separate description of the operative technic; it will be presented as it was carried out in this patient.

REPORT OF A CASE

J. S., an otherwise healthy woman of 29, had been admitted to the peripheral vascular disease clinic of the Massachusetts General Hospital for Raynaud's afflictions of the upper extremities. This operation, which has been developed by Smithwick,⁶ was performed in two stages through posterior paramedian incisions, with removal of short lengths of the central ends of the third ribs and the third thoracic ganglion, and its cephalic end was drawn up and buried in the second intercostal muscle. In order to interrupt additional vasoconstrictor fibers which entered in the second and third intercostal nerves, Dr. Smithwick at first resected short segments of these two nerves at their point of exit from the intervertebral foramina, the portion which gives off the sympathetic rami communicantes. Experience with this method soon taught that regeneration of the vasoconstrictor fibers would take place unless the intercostal nerves were freed centrally far enough to permit resection of a portion of their anterior roots. Regeneration of vasoconstrictor activity with recurrent manifestations of Raynaud's disease took place in this woman within six months, and the symptoms were so severe that she demanded further operation. In an attempt to secure permanent interruption of the vasoconstrictor fibers, Dr. Smithwick reoperated on several occasions and attempted to resect the cicatricial tissue and sympathetic fibers regenerating from the intervertebral foramina.⁷

In September 1937, after these operations, the patient began to complain of neuralgic pain down the inner side of the upper part of the right arm and in the right axilla.⁸ In its early stages the pain was confined to the territory of the divided nerve trunks, but by the autumn of 1938 it was beginning to involve more of the right arm and breast and was becoming increasingly severe. It was observed that on the painful side the patient had a warm, dry hand, whereas the left hand was frequently cold, moist and cyanotic. After consultation (requested by Dr. Smithwick) she was admitted to the neurosurgical service for spinal root section.

On Oct. 4, 1938, laminectomy was performed, with section of the posterior sensory roots of the second and third intercostal nerves on the right (neuralgic) side and of the corresponding anterior motor roots on the left, in the hope of securing permanent interruption of the vasoconstrictor fibers. As the second and third intercostal nerves were the only ones which could have been exposed to trauma at Dr. Smithwick's previous operations, we had anticipated that division of their sensory roots would bring relief from the neuralgic pain. In this we were completely mistaken, and her pain was in no way alleviated, although circulation in the hand has continued at a maximum on the side where the anterior roots with their vasoconstrictor fibers were cut. The neuralgia not only persisted but increased in severity and spread to involve the entire arm, upper part of the chest, neck and occiput on the right side. This area became hyperesthetic and so painful on touch or movement that the patient was no longer able to use the arm and had to hold it constantly in a guarded position. During the past summer she

6. Smithwick, R. H.: Surgical Intervention on the Sympathetic Nervous System for Peripheral Vascular Disease, *Arch. Surg.* 40:286-306 (Feb.) 1940.

7. The circulatory aspects of the case of J. S. have been summarized by Smithwick.⁶

8. Neuralgia following this operation has never been observed in any other patient.

required increasing doses of codeine sulfate and phenobarbital and stated on numerous occasions that self destruction would be preferable to her neuralgic pain.

In this highly neurotic condition she was seen in consultation by Dr. Stanley Cobb, chief of the psychiatric service, who stated that in his opinion her pain was an organic neuralgia and not of functional origin. The possibility of relieving this high cervical and brachial neuralgia by cutting the spinothalamic tract in the medulla was then discussed with the patient, with an explanation of the risks of injury to contiguous structures. She accepted this without hesitation and furthermore agreed that she would do everything in her power to go through the operation under local anesthesia, in order to make certain that the section should be carried to a sufficient depth to insure analgesia to the first cervical segment.

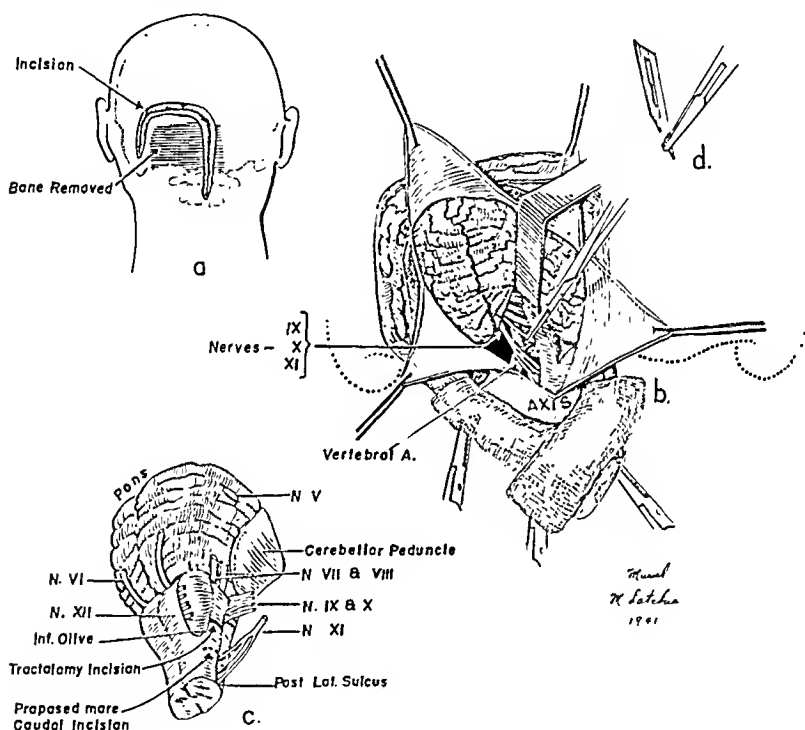


Fig. 5.—Technic of spinothalamic tractotomy in the medulla. *a*, scalp incision and extent of occipital bone to be removed. *b*, exposure of the structures at the side of the medulla and insertion of the knife in the posterior lateral sulcus. *c*, medulla and pons viewed from below and from the side to show the relation of the tractotomy incision to the vagal rootlets and the inferior olive. In future cases it is planned to divide the tract at a more caudal level, indicated by the broken line. *d*, adaptation of the pointed Bard-Parker blade into a chordotomy knife. The large central portion of the blade is broken off, leaving only 4 mm. of tip protruding from the hemostat.

This operation was performed on Oct. 9, 1940, with the patient in the prone cerebellar position. After preliminary infiltration of procaine hydrochloride solution (1 per cent, with epinephrine hydrochloride) into the occipital region and along the posterior borders of both sternocleidomastoid muscles, a cerebellar

incision was made in the scalp on the left side and the occipital bone rongeur'd away from 2 cm. to the right of the midline to a point just medial to the mastoid air cells on the left side and from the insertion of the occipital muscles above down into the foramen magnum below (fig. 5 *A*). The dura over this area was opened widely and the cisterna magna drained. On elevating the cerebellar tonsil it was then possible to obtain a clear view of the side of the medulla and the roots of the spinal accessory, vagus and glossopharyngeal nerves at their points of exit from the upper cervical portion of the cord and the posterior lateral sulcus of the medulla (fig. 5 *B*). The point selected for making the section lay just below (caudal) and ventral to the last vagal rootlet (fig. 4 *C*). My purpose had been to incise to a depth of 4 mm. straight inward from this point and anteriorly to the inferior olive, but the large trunk of the vertebral artery obscured the lateral bulge of the olive. In addition, another good-sized arterial trunk lay just below the emerging vagal rootlets and adhered to the surface of the medulla (figs. 2 *A* and 3). This must have been a large branch of the posterior inferior cerebellar artery. At first it looked as though it would be impossible to dislodge it and make the cut at the necessary point, but by gentle wiping with a wisp of cotton held in a thin-bladed forceps it was finally possible to displace it forward. It was then a relatively simple matter to make the incision in the posterior lateral sulcus (fig. 5 *C*). The vagal rootlets mark this point and are just as satisfactory a marker as the dentate ligament in the cord, except that they can be neither grasped nor stretched with impunity. A good instrument for making this incision is a pointed Bard-Parker knife blade held at right angles in a small hemostat and broken off so that the point protrudes exactly 4 mm. (fig. 5 *D*). Using this instrument, I thrust the point directly inward just short of its measured depth and cut ventrally down to the vertebral artery, which obscured the lateral edge of the inferior olive. By angulating the point still farther inward and ventrally I felt that I was able to carry the cut well down to the level of the olivary nucleus (figs. 2 *B* and 5 *C*). The patient, who remained fully conscious, was then tested, and a sensory level was established at the shoulder girdle. The knife blade was then reinserted to its full depth. After this it was found that pricking with a needle was no longer painful in the shoulder and neck. During the first cut she had made no mention of any painful sensation, but the second time the knife entered at the posterior lateral sulcus she complained momentarily of a sharp sensation in the ipsilateral side of her face—presumably from touching the ventral fibers of the descending trigeminal tract. This and some twinges of pain referred to her ear as the vagal rootlets were put on a stretch were the only sensations which she mentioned. As soon as the spinothalamic tract on her left side had been cut she could tell that the pain in her right arm had vanished. The cut caused almost no bleeding, and by additional good fortune it had been possible to keep the field dry throughout this critical part of the operation. The patient's pulse and blood pressure had remained steady throughout the procedure. A routine closure of the muscles, fascia and skin was carried out with multiple layers of interrupted silk sutures, and the patient was returned to her bed in excellent condition.

Recovery from operation was uneventful except for headache lasting five days and a mild depressive psychosis. It was difficult to persuade her to take adequate amounts of liquids and solids or to resume normal physical activity, but this abnormal behavior was less exaggerated than after previous operations. She urinated spontaneously on the evening of the day of operation and noted no difficulty in swallowing and no change in the quality of her voice. During her early convalescence it was impossible to detect any evidence of injury to the cranial nerves or to the spinal pathways other than the spinothalamic tract. In view of

the fact that during the tractotomy she had complained of pain in the left side of her face (indicative of trauma to the descending trigeminal tract), it is surprising that no change in pain or thermal sensation could be discovered in this area afterward. She was discharged from the hospital relieved of her old complaints on the twenty-fourth day after operation.

As long as the patient remained in bed no signs of injury to cerebellar function were observed except for very slight past pointing to the left (the side on which the brain stem was incised). After she became ambulatory, however, she complained of a sense of forced swaying to the left, so that in walking she had to prevent herself from falling by touching a wall or holding another person's arm. When she returned to the hospital for reexamination, three months later, her gait was still too unsteady to permit her to walk across a room without support. There was also a tendency to past point about 1 inch (2.5 cm.) to the left in lowering her arm from a vertical to a horizontal position with her eyes closed. When she was "off her feet" all sensation of unsteadiness disappeared and she was able to carry on complicated synergic movements, such as typing, with her former facility.

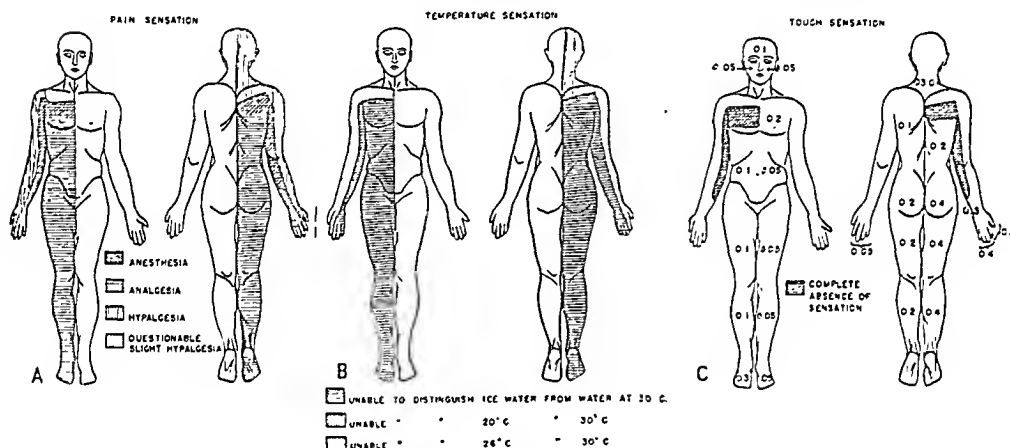


Fig. 6.—Results of tests for pain, temperature and touch. The figures are recorded in grams and represent the minimal pressure of Frey's hairs which could be felt. *A* and *B*, tests made on Oct. 23, 1940. *C*, test made on October 24. See text for fuller explanation.

(This difficulty in gait, even if it lasts, should not interfere with any occupation at which the patient can remain seated. It is probable that it will disappear in time, as is usually the case after such severe disturbances following injury to the lateral cerebellar structures by abscess of the brain or trauma, but it must be admitted that the improvement to date has been slight.)

From the moment the spinothalamic tract was cut the long-standing neuralgia disappeared. At the time of writing, analgesia and thermoanesthesia have remained complete below the sixth cervical segment, and there has been a definite reduction in these modalities of sensation as high as the first cervical segment. The patient is convinced that she remains fully relieved and fails to detect any disagreeable sensation on using her arm or on strenuous massage of the hitherto hypersensitive area in the upper part of her chest, her arm and her neck.

Before her discharge from the hospital, careful neurologic tests were performed to determine changes in the various forms of sensation over her entire

body. Tests for discrimination of pain, temperature and touch were carried out in a rough quantitative manner, and the results are shown in figure 6. These show complete anesthesia over the second and third thoracic spinal nerves on the right side, corresponding with the previous posterior rhizotomy. As a result of section of the spinothalamic tract, pain and temperature sensation have been completely interrupted below the sixth cervical segment and impaired over the posterior part of the scalp and the neck, but only to a minor degree over the front of the neck, shoulder and outer arm (fig. 6A and B). Figure 6C shows only a minimal reduction in tactile acuity (measured by the Frey hairs) on the side deprived of its spinothalamic innervation. This difference was too slight for the patient to notice subjectively. No change in deep pressure, vibration or position sense could be made out. These tests were repeated at her subsequent admission (three months after operation) and showed no recovery of sensation. The changes are consistent with the well known effects of cutting the pain and temperature pathway in the spinal cord.

COMMENT

The operation described was the first recorded successful spinothalamic tractotomy carried out in the medulla oblongata. Credit for suggesting this procedure belongs to Drs. Schwartz and O'Leary,⁹ of St. Louis. Although the first patient operated on by Dr. Schwartz failed to recover, the period of survival was long enough to demonstrate a satisfactory high loss of pain and temperature sensation without any serious injury to neighboring tracts and nuclei. It is of particular interest to know that this patient left her bed unassisted a few hours after operation without any disturbance in gait being recorded. In Sjöqvist's trigeminal tractotomy there is a definite risk of producing cerebellar disturbances due to the propinquity of the descending trigeminal tract to the inferior cerebellar peduncle (Rowbotham⁹). Involvement of this sort after the more ventral incision of the brain stem which was used to divide the spinothalamic tract was not anticipated. Whether it was due to injury of the restiform body, to the olivocerebellar fibers or to their blood supply is not certain. As Grant and Weinberger¹⁰ have found that disturbances of this sort after section of the descending spinal trigeminal root can be reduced by making a more caudal incision, it will be advisable to try this modification in the future. The incision, instead of being made ventral to the posterior lateral sulcus just caudal to the last emerging vagal rootlet, should be placed 5 to 8 mm. caudal to this point, i. e., just below instead of just above the tip of the fourth ventricle (obex). Although it is probable

9. Rowbotham, G. F.: Treatment of Pain in the Face by Intramedullary Tractotomy, *Brit. M. J.* 2:1073-1076, 1938.

10. Grant, F. C., and Weinberger, L. M.: Experiences with Intramedullary Tractotomy: I. Relief of Facial Pain and Summary of Operative Results, *Arch. Surg.* 42:681-692 (April) 1941.

that postoperative cerebellar disturbances will disappear spontaneously in time, they are a serious defect in a person who is able to lead an active life.

I have compared notes about the operation with Dr. Schwartz, and both of us have reached the conclusion that the landmarks for cutting the tract are just as well defined in the medulla as in the spinal cord. The pyramidal tract is protected by the interposed mass of the inferior olive. In medullary tractotomy care must be taken not to traumatize the vagal rootlets, which has resulted in temporary inferior laryngeal paralysis in some cases of descending spinal trigeminal root section reported by Sjöqvist.⁴ As far as is known, injury to the neighboring rubrospinal tract or to either the main inferior olivary nucleus or the dorsal accessory olive will not cause any serious disturbance. Whether injury to the nucleus ambiguus from too deep a section would result in difficulties in swallowing is not certain, but, since this nucleus is a relatively long structure, injury to a small group of its motor neuron cells should not result in any lasting disability. Other uncertain points are the exact position of the motor fibers to the bladder and the risk of injuring them. In this case the patient voided spontaneously within a few hours of the operation. The fact that the patient did not have Horner's syndrome or any alteration in sudomotor or vasomotor activity shows that the incision did not penetrate the reticular substance to a sufficient depth to injure the descending sympathetic fibers which are supposed to lie in this area (List and Peet,¹¹ Foerster,¹² Magoun¹³). Judging from this single experience, it would not seem that spinothalamic tractotomy in the medulla offers any great difficulty or danger, and it is quite possible that it may prove to be as simple a procedure as section of the tract in the spinal cord.

The one major difficulty encountered by both Dr. Schwartz and myself lay in dealing with the vessels that lie alongside this region of the medulla. In this patient a large vertebral artery obscured the bulge in the medulla that marks the inferior olive and so filled the space between the medulla and the bony wall of the foramen magnum that it could not be dislodged (fig. 3). There was another awkward arterial trunk of considerable size which ran just ventral to the glossopharyngeal and vagal rootlets and was adherent to the side of the medulla at the

11. List, C. G., and Peet, M. M.: Sweat Secretion in Man: V. Disturbances of Sweat Secretion with Lesions of the Pons, Medulla and Cervical Portion of Cord, *Arch. Neurol. & Psychiat.* **42**:1098-1127 (Dec.) 1939.

12. Foerster, O.: Die vegetativen supranuclearen Bahnen und die Reflexe der vegetativen Sphäre, in Bumke, O., and Foerster, O.: *Handbuch der Neurologie*, Berlin, Julius Springer, 1936, vol. 5, p. 213.

13. Magoun, H. W.: Descending Connections from the Hypothalamus, *A. Research Nerv. & Ment. Dis., Proc.* (1939) **20**:270-285, 1940.

point where the section had to be made. This appeared to be a large branch of the posterior inferior cerebellar artery. In addition to this there were a number of smaller vessels, one of which was clipped and cut. It was finally possible to wipe the larger artery out of the way. Had this not been the case or had it been injured and bled, I believe that it could have been clipped without causing widespread ischemia of the medulla, because the point for introduction of the cordotomy knife lay below (caudal to) its important tributary branches to the inferior cerebellar peduncle (restiform body) and the vestibular nuclei. The importance of handling these vessels skilfully to insure complete hemostasis and to avoid profuse bleeding, which might involve serious trauma to the medulla and its cranial nerve roots, cannot be overemphasized. Routine inspection of this region in all the operations on the posterior fossa performed during the past five months has convinced me that the lateral surface of the medulla down to the bulge of the olive can be safely exposed in the average patient but that in an exceptional case in which the blood vessels are unusually large this step may be extremely difficult.

One further point deserving consideration is the reason for the incomplete loss of pain and temperature sensation above the seventh cervical segment. This fortunately turned out to be for the best, as the patient retained these forms of sensation in the outer part of the arm, the neck and the scalp to a large degree, but with loss of her former hyperesthesia in these areas. The explanation for this incomplete loss must depend on the anatomic arrangement of the pain fibers in the spinothalamic tract. According to Foerster,¹⁴ the fibers are arranged in a laminated fashion, those from the lowermost segments of the body occupying a place at the periphery of the tract and those of the higher segments remaining closer to the central gray matter (fig. 7 A). If this theory is correct, one must conclude that cutting to a depth of 4 mm. was not deep enough to secure complete interruption of the central portion of the tract. On the other hand, Hyndman and Van Epps¹⁵ and also Walker² have presented evidence in favor of a different composition of the tract. According to them, the fibers from the lowest body segments lie in the more dorsal portion of the tract, whereas those from higher segments are more ventrally placed (figs. 7 B and C). In describing the spinothalamic tract in the bulb Walker stated that "there is both anatomical and clinical evidence for suggesting a topical arrangement within the tract at this level. The fibers which carry sensory

14. Foerster, O.: *Die Leitungsbahnen des Schmerzgefühls und die chirurgische Behandlung der Schmerzzustände*, Berlin, Urban & Schwarzenberg, 1927.

15. Hyndman, O. R., and Van Epps, C.: Possibility of Differential Section of the Spinothalamic Tract, *Arch. Surg.* 38:1036-1053 (June) 1939.

impulses from the caudal parts of the body lie laterally (peripherally) and dorsally; those from the head are more medially and inferiorly situated." As the exact level of the olive, which marks the ventral limits of the tract, was obscured by the vertebral artery, it is quite possible that these most ventrally situated fibers were not completely divided. Until this problem is settled it will be essential to perform this operation under local anesthesia and to make progressively deeper and more ventral sections into the medulla until the desired sensory level is obtained.

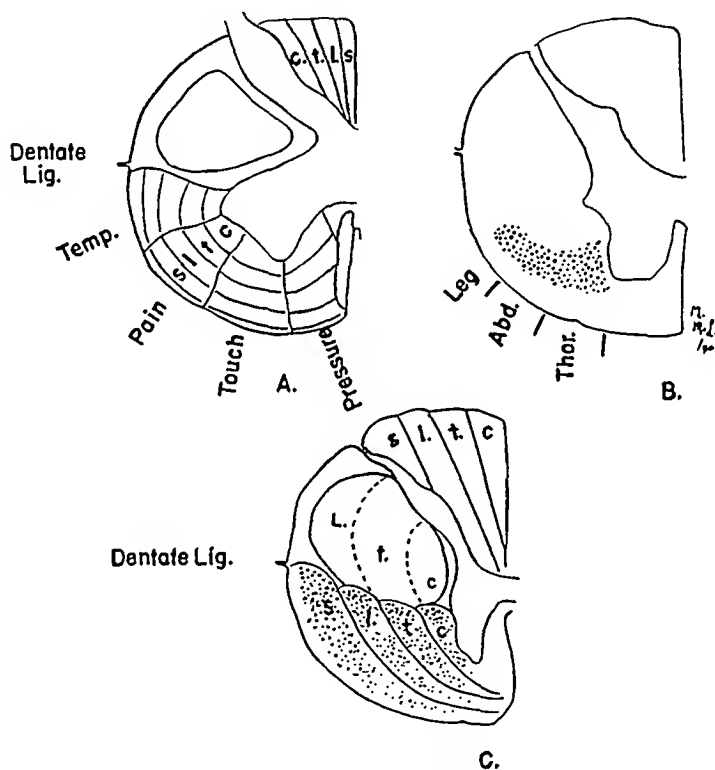


Fig. 7.—Anatomic composition of the spinothalamic tract according to: (A) Foerster; (B) Hyndman and Van Epps and (C) Walker. Abbreviations used in representing the segmental fibers: *c*, cervical; *t*, thoracic; *l*, lumbar; *s*, sacral. In Walker's diagram the heavy stippling in the most dorsal portion of the spinothalamic tract represents the hypothetical position of the temperature fibers. The most medial and ventral fibers are supposed to carry touch and pressure impulses.

Intramedullary section of the spinothalamic tract should make it possible to relieve a number of hitherto intractable painful syndromes of the shoulder, neck and occiput. These include the neuralgias which may follow amputation of the upper extremity and avulsion of the brachial plexus, and certain obscure painful states which occasionally develop after penetrating injuries and operations in this area. Even

the most extensive resection of posterior spinal roots has usually failed to relieve these conditions. This has likewise been the unfortunate experience in cases of painful paralysis of the arm resulting from carcinoma of the breast invading the brachial plexus or from carcinoma of the apex of the lung with regional nerve involvement and in cases of the lightning pains of tabes. Similar pathologic conditions which give rise to pain in the trunk or lower extremity, however, are amenable to chordotomy. Unfortunately, when pain spreads into the shoulder and neck the spinothalamic tract cannot often be divided high enough in the cord to interrupt its fibers to the upper cervical dermatomes. But if the tract is sectioned in the medulla as described, the sensation of pain can be abolished as high as the first cervical segment. In addition, when a useful arm can be preserved its function is but little impaired by the loss of pain and temperature sensation, while it is rendered practically useless by the total anesthesia which follows cutting the sensory spinal roots.

CONCLUSIONS

Experience with the case described in this paper and the cases which have been reported by Schwartz and O'Leary indicates that section of the spinothalamic tract high enough to produce hemianalgesia to the first cervical segment is a practical operation. The lateral wall of the medulla can be easily reached through unilateral removal of the occipital bone down to the foramen magnum. At this level the spinothalamic tract lies between the vagal rootlets emerging from the posterior lateral sulcus and the inferior olive. The posterior inferior cerebellar and vertebral arteries require most careful manipulation. From a limited experience it would seem as though the technical hazards involved in this operation will depend on the difficulty encountered in dealing with these structures. If the vascular arrangement in this single case is typical, the operation will be practical for the average patient, although not too easy. The landmarks for sectioning the spinothalamic tract are just as clearcut in the medulla as in the spinal cord, and the risk of injury to the pyramidal tract is less than in the well standardized spinal procedure. It must be recorded that in this patient after long survival there still remains a troublesome cerebellar ataxia. In future tractotomies of this type the incision in the medulla must be made at a more caudal level in order to avoid damage to the nerve fibers and blood supply of the restiform body.

NOTE.—After this article was written a similar operation was performed by Dr. Donald Munro, of the Boston City Hospital. His patient, a middle-aged man, had metastatic carcinoma of the neck with intractable pain in the neck, shoulder and arm. For this, section of the posterior

roots of the cervical nerves had been performed. This operation, as is so often the case, had failed to relieve his pain. Dr. Munro sectioned the spinothalamic tract in the medulla in February 1941, using the exact technic described in this article. The patient made an uneventful convalescence without the development of any complicating cerebellar ataxia. At the end of four months he remained completely free of his pain and was not taking any narcotic medication.

REVIEW OF UROLOGIC SURGERY

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KIDNEY

Tumor.—Gillies¹ studied 50 cases of verified malignant tumor of the kidney in adults.

Tumors primary in the renal pelvis were found in 10 per cent of the cases. In this group intermittent hematuria was the first symptom in each case. Accompanying stones were present in only 1 case.

With small and moderate-sized tumors, pyelograms show irregular filling defects without distortion of the renal outline.

Large tumors invading the kidney cannot be distinguished from primary tumors of the kidney invading the renal pelvis.

Malignant tumors primary in the kidney were present in 90 per cent of the cases of this series. These occurred in men nearly three times as frequently as in women.

In plain roentgenograms, changes in size, shape and density of the kidney, as well as calcium deposits, which occurred in 38 per cent of the cases in which roentgenograms of the kidney were made, should be looked for.

1. Gillies, C. L.: Malignant Tumors of the Kidney in Adults, *Am. J. Roentgenol.* **43**:629-635 (May) 1940.

Retrograde pyelograms in the presence of tumor show most frequently elongation and compression of one or more of the major calices. Less commonly, there may be complete loss of the normal pelvic landmarks, and rarely, dilatation of the pelvis accompanied with elongation and dilatation of the calices without remarkable compression.

Elward and Spire² reported a case of bilateral hypernephroma. In this case there were no subjective symptoms referable to the genitourinary tract. The disease metastasized early to the mediastinum, where all the symptoms seemed to originate. The metastatic growths responded rapidly to roentgen therapy and almost as rapidly became radioresistant. The outcome was fatal. The possibility of cancer of a so-called renal rest of the mediastinum with metastasis to both kidneys must be considered.

Hayward³ reported a case of malignant papillary cystadenoma. The tumor produced no symptoms; in spite of its enormous size the patient did not know of its presence. It had been present for a long period and was of low malignancy. It was discovered during a physical examination made for an acute cardiac condition of which the patient died within twenty-four hours of his admission to the hospital. The tumor apparently had nothing to do with his death. Permission for a complete postmortem examination was refused; so the presence or absence of metastatic growths could not be determined.

Kretschmer,⁴ in a discussion of adenomyosarcoma of the kidney (Wilms tumor), stated that although a few cases have been reported in which the tumor occurred in an adult, the fact remains that it is essentially a disease of infancy and childhood. As a rule it runs a silent and rapid course, as is evidenced by the fact that it reaches a large size before medical aid is sought. The histologic picture is unique. The outcome is generally fatal. A multiplicity of theories has been advanced from time to time regarding the pathogenesis.

The sex incidence is of little aid in the diagnosis. In Kretschmer's previous studies 18 patients were boys and 6 were girls. In the 3 cases that form the basis of this paper all the patients were boys. It would appear, therefore, that boys (77.77 per cent) are more frequently afflicted than are girls.

The Wilms tumor is predominantly unilateral. Bilateral tumors have been reported, but they are uncommon. Kretschmer had observed

2. Elward, J. F., and Spire, R. L.: Bilateral Hypernephroma, *Radiology* **35**:274-281 (Sept.) 1940.

3. Hayward, W. G.: Malignant Papillary Cystadenoma of the Kidney: Case Report, *J. Urol.* **44**:259-263 (Sept.) 1940.

4. Kretschmer, H. L.: Adenomyosarcoma of the Kidney (Wilms Tumor): Report of Three Cases, *Arch. Surg.* **41**:379-384 (Aug.) 1940.

2 such growths. The tumor varies greatly in size. The smallest tumor seen by Kretschmer weighed 235 Gm. The growth may nearly fill the abdomen and extend into the pelvis so that it can be felt on rectal examination. This occurred in 2 of the 3 cases reported in this paper. There may be displacement of viscera. The tumor may take its origin from either the upper or the lower pole or from the middle of the kidney. It is encapsulated; it is globular or oval, and it often appears lobulated. The surface is generally smooth, although a nodule may protrude above it. The kidney is separated from the tumor by a sharp line of demarcation. The kidney is compressed by the growth and suffers from pressure atrophy. The renal pelvis also is compressed, except in the rare instances in which the tumor seems to grow around the pelvis. In Kretschmer's experience the tumor was solid. In none of his cases did it have the appearance of a polycystic kidney, although this appearance has been mentioned in the literature.

That this sort of tumor runs a relatively silent course is unfortunate for the patient, since in many cases treatment is sought too late for surgical relief, as was instanced in 2 of the 3 cases reported in this paper. Another drawback is the fact that symptoms referable to the urinary tract are absent, except possibly in the rare cases in which hematuria is present. Likewise, pain is a relatively uncommon symptom and occurs late in the course of the disease. Anemia and loss of weight are late manifestations.

As a rule the diagnosis presents no difficult problem. The presence of an abdominal tumor which has increased rapidly in size and is hard, sometimes nodular and nearly always painless, coupled with the fact that the commonest abdominal tumor occurring in children is the Wilms tumor, should lead to a tentative diagnosis of that tumor in the case of every child with an abdominal growth. The diagnosis is further strengthened by changes in the pyelogram compatible with tumor. In every case in which a tentative diagnosis of Wilms tumor is made, a plain roentgenogram of the abdomen is taken to rule out stone in the urinary tract. The next step in examination consists of obtaining a set of intravenous urograms. Occasionally there may be complete failure to visualize the renal pelvis on the affected side, although the opposite pelvis is shown as normal. But, on the other hand, the pyelogram is frequently most dependable.

A good many differences of opinion still exist as regards the best form of treatment. McNeill and Chilko,⁵ in a survey of 383 cases, found that six types of treatment had been followed: (1) nephrectomy

5. McNeill, W. H., Jr., and Chilko, A. J.: Status of Surgical and Irradiation Treatment of Wilms' Tumor and Report of Two Cases, *J. Urol.* 39:287-302 (March) 1938.

alone; (2) the use of serum in conjunction with nephrectomy; (3) roentgen therapy to reduce the size of the tumor and kill the embryonal cells, followed by nephrectomy; (4) roentgen therapy followed by nephrectomy and by another course of roentgen treatment; (5) nephrectomy followed by postoperative roentgen treatment to destroy any residual malignant embryonal cells, and (6) roentgen treatment alone. They reported the case of 1 patient alive and well three years after irradiation.

At the time of Kretschmer's report the routine followed by him and his associates was to give the patient a course of high voltage roentgen therapy followed by nephrectomy, after which another course of high voltage roentgen therapy was carried out. In his experience, not all Wilms tumors are radiosensitive. When the growth is radiosensitive and shows a marked reduction in size, nephrectomy is simplified. With the diminution in size of the tumor, corresponding changes are observed in the pyelogram. Attention was called to this phenomenon in a previous publication.

Awareness that malignant tumors of the kidney are common in animals and that these tumors are closely similar to renal cancers in man led Lucké⁶ to carry out experimental studies on a certain type of renal cancer in frogs. This is a typical invasive and metastasizing adenocarcinoma. The mechanics of growth of this cancer have been investigated by transplanting it into the anterior chamber of the eye, where its mode of development has been followed by direct and continued observations with the microscope. It was thus learned that the form of the growing tumor depends on the immediate physical environment and that growth takes place according to well defined structural patterns. This conclusion was supported by study of the characteristics of growth of the tumor in tissue culture.

Lucké also discussed the modifying influence of temperature on the growth of cancer and showed that temperature affects the rate and character of cancerous growth in much the same general way as it affects growth of normal tissues.

It is concluded that cancer obeys the physical laws governing normal growth far more than is commonly supposed; neoplastic growth is certainly not lawless.

Calculus.—Gutierrez⁷ stated that the possibility of a silent renal stone too frequently is overlooked by clinicians who are handling anemia

6. Lucké, B.: Physical Factors Influencing the Growth of Cancer. Experimental Studies Based on Renal Adenocarcinoma in Animals. *J. Urol.* **44**:545-558 (Nov.) 1940.

7. Gutierrez, R.: The Significance of Silent Kidney Stone in Anemia. *M. Rec* **152**:288-292 (Oct. 16) 1940.

that proves refractory to the usual modes of treatment. While the extent of "silent" renal derangements is well understood by the urologist, it is unfortunate that the internist does not always bear equally in mind, when he is consulted by an anemic patient, that an infected stone in the kidney or in the ureter may run a long silent course and cause marked secondary anemia without producing any urinary symptoms whatever. When simple urinalysis shows nothing suspicious, it too often is assumed that both kidneys are in good condition and that the cause of the anemia does not lie within the urinary tract.

Urologic experience proves, however, that there are many types of renal pathologic processes that do not for a long time reveal their presence through simple urinalysis. Several types of silent renal stone associated with anemia can be readily recognized.

Patients carrying silent renal stones must receive suitable operative intervention, which demonstrates the effect of removal of stone on the general health. Patients who have infected renal stones are carrying a latent focus of infection and are suffering from the effects of general toxemia and septic absorption, which in the course of time will affect the hemopoietic organs and betray itself as stubborn anemia. The renal stone may remain silent for a long time, during which it produces constitutional symptoms long before any local symptoms within the urinary tract betray its presence.

It is obvious that if a stone is impacted painlessly within a ureter or a renal pelvis in such a way as to block completely the escape of urine on one side, all the urine obtained comes from the kidney of the opposite side, which may be sound. In a case of this kind the results of urinalysis are indecisive. Nonopaque stones that do not appear in the plain roentgenogram may be revealed by a filling defect in the retrograde pyelogram. -

Randall⁸ stated that primary renal calculus is only a symptom and always originates as a slow crystallization of urinary salts on a lesion of the renal papilla. He presented evidence that calcium phosphate, calcium oxalate and uric acid crystallization, to form renal calculi, had in each example which he studied been deposited on a plaque of calcium salts deposited in the renal papilla.

Randall expressed the belief that pathologic change in the papilla precedes the development of a primary renal calculus and acts as the initiating lesion on which these urinary salts crystallize.

It is worthy of mention that calculi supposed to be associated with hyperparathyroidism, hypovitaminosis, odd forms of renal infection and nephrocalcinosis belong to a separate and different form of pathologic

8. Randall, A.: Papillary Pathology as a Precursor of Primary Renal Calculus, *J. Urol.* **44**:580-589 (Nov.) 1940.

alteration of the papilla, associated with tubular inspissation of salts (calcium infarction), and represent the end results of hyperexcretory states.

Rosenow⁹ studied the kidneys in 239 consecutive necropsies. The study was limited to examination of the papillae for calcareous deposits and in some instances for the presence of bacteria.

Usually the microscopic appearance of the calcareous plaques was that of an irregular mass of deep purple-staining material lying in the interstitial tissue. If the plaque was near enough to the surface there was some loss of epithelial continuity. At times the plaque was covered with only a thinned-out single layer of epithelium. In some tubules the calcium seemed to be deposited in the epithelial cells. In many cases bits of calcareous material were found in the medulla. Seldom was calcium found in the ureter. There was practically no evidence of active infection in regions near the calcareous deposits. Rosenow expressed the opinion that probably these calcareous plaques do not initiate formation of stone unless they are so situated as to be in communication with the pelvis of the kidney.

In the study for bacteria, organisms were difficult to find, and they were never found except close to regions of calcification. Almost all the organisms discovered were either diplococcic or streptococcic. Although bacteria were observed in close proximity to regions of papillary calcification, there was practically no evidence of active inflammation. The absence of active inflammation should not minimize the importance of discovering bacteria. If calcification is the end result of damage to tissue, one would not expect to find any evidence of active inflammation, such as collections of leukocytes or lymphocytes.

In this study of the kidneys in 239 consecutive necropsies, plaques of calcareous material were found in the renal papillae in 53 (22.2 per cent) of the cases. Calculi were found in 13 (5.4 per cent) of the cases; they were adherent to the papillae in 5 cases. Bacteria were present in 24 (64.9 per cent) of 37 cases in which examination for bacteria was made. Microscopic intramedullary calcification was present in only 4 of 24 control sections of papillae without grossly visible papillary plaques. Age, sex, grade of arteriosclerosis and necropsy diagnosis were not important factors.

Tuberculosis.—Henline¹⁰ presented a résumé of 40 cases in which a diagnosis of bilateral renal tuberculosis had been made.

9. Rosenow, E. C., Jr.: Renal Calculi: A Study of Papillary Calcification. *J. Urol.* **44**:19-28 (July) 1940.

10. Henline, R. B.: Surgery of So-Called Bilateral Renal Tuberculosis. *South. M. J.* **32**:1185-1199 (Dec.) 1939.

The difficulties of making an accurate diagnosis were stressed. Cystoscopic examination is often difficult or impossible, owing to marked involvement of the bladder. Ureteral catheterization was impossible in 14, or 35 per cent, of the cases.

Tubercle bacilli were found in the vesical urine (by smear or guinea pig inoculation) in 36 of the cases.

To make a diagnosis reliance must be placed on urographic study, assisted occasionally by the finding of tubercle bacilli in the vesical urine.

Examination of 29 kidneys removed at operation and of kidneys removed at necropsy in 4 cases revealed tuberculosis in all.

At the time the résumé was presented, 21 of 29 patients had lived an average of five and four-tenths years after removal of the more infected kidney in the presence of so-called bilateral renal tuberculosis. Seven had died, after living an average of five and fifteen-hundredths years; 1 patient could not be followed.

Eight of 11 patients had lived an average of seven and fifty-six-hundredths years with medical treatment alone. One died two and a half years after treatment was begun, and trace of 2 was lost.

Patients treated by medical means alone manifested as a rule a clinically different type of renal tuberculosis (fibrotic). A few destructive lesions thus treated (rare) had shown no demonstrable progression.

Ten, or 47.6 per cent, of the living patients who had been operated on showed marked improvement in the condition of the bladder or were practically cured after removal of the worse kidney, while 13, or 61.9 per cent, evidenced general improvement. Four, or 50 per cent, of those treated medically alone showed improvement in the condition of the bladder, and 5, or 62.9 per cent, improvement in general health.

In 1 case in which a diagnosis of tuberculosis in the remaining kidney had been made, the patient, a woman, had undergone transplantation of the ureter to the sigmoid flexure of the colon four years prior to Henline's report, with complete relief of intolerable vesical pain.

Prompt removal of an obviously destroyed kidney is justified provided the function of its mate is sufficient, as this is the method of treatment which offers the greatest hope of relief.

Tuberculosis of the urinary tract was a local disease in 25 of the 40 cases, with no evidence of active lesions elsewhere in the body.

So-called autonephrectomies may be closed off from the bladder, but the renal lesion usually remains pathologically active and, being a focus of infection, should be removed.

The hydronephrosis and hydroureter which frequently develop in the better kidney may be the result of primary tuberculosis of the kidney or may be secondary to a ureteral stricture.

Medical care by an experienced internist is indispensable in the post-operative care of bilateral renal tuberculosis as well as in the treatment of patients suffering from bilateral inoperable tuberculosis.

Pyelonephritis.—Mussey and Lovelady¹¹ stated that acute pyëlitis of pregnancy increases the hazards to both the mother and the fetus. If the disease is recognized early and treated promptly, the hazard is lessened.

Among 121 cases of pyelitis the incidence of spontaneous abortion and premature labor was 4.9 per cent; in 7 cases (5.7 per cent) labor was induced, but this procedure was not found to be necessary prior to the period of viability. In 21 per cent of the cases in this series pyelitis first became evident after delivery. This is an incidence of approximately 0.4 per cent of all confinement cases, and it is obvious that pyelitis should be suspected in cases of otherwise undiagnosed postpartum fever. The findings in this series indicate that acute pyelitis of pregnancy is rarely either the indirect or the direct cause of preeclamptic toxemia and eclampsia.

Evidence indicates that in a majority of cases pyelitis will respond promptly to rest in bed, administration of sedatives and forcing of fluids and that when pyelitis of pregnancy is recognized early and treated adequately few patients will require drainage by ureteral catheter for relief. Favorable results have been obtained recently in a few cases by the administration of preparations of mandelic acid or sulfanilamide. Occasionally drainage with the ureteral catheter is of value in treating acute persistent pyelitis of pregnancy in combination with chemotherapy and other measures.

Injuries.—Sargent,¹² in discussing injuries of the kidney, stated that immediate examination of urine, either voided or catheterized, must be made absolutely routine in all cases of accident. Considering the danger that lurks in hemorrhage and particularly the terrible consequences of urinary extravasation when it occurs, altogether too much is at stake to neglect this simple and easy precaution.

Gross hematuria in cases of accidental injury demands absolutely accurate diagnosis. Many times it proves to be of no particular consequence, but many times also it bespeaks an injury of the first magnitude.

Intravenous urographic examination can be fairly useful as a scout procedure in those cases of accident in which injury to the urinary tract

11. Mussey, R. D., and Lovelady, S. B.: Pyelitis of Pregnancy and Its Management in One Hundred and Twenty-One Cases, *West. J. Surg.* **48**:591-596 (Oct.) 1940.

12. Sargent, J. C.: Injuries of the Kidney with Special Reference to Early and Accurate Diagnosis Through Pyelography, *J. A. M. A.* **115**:822-825 (Sept. 7) 1940.

is suspected. It must be followed by more exact studies, however, unless sharp outline permits quite exact interpretation and even then if substantial injury seems to be present.

Finally, Sargent reiterated that it is only in the retrograde pyelogram that one can find substantial, dependable and consistent help in determining when and when not to operate on a kidney that has been injured.

Henline¹³ stated that retrograde pyelographic examination for suspected renal injury, done under sterile precautions, should afford more accurate information regarding the extent of the renal damage. Use of the newer contrast mediums for pyelography, which readily and harmlessly diffuse with the blood, should add no additional hazard to a ruptured kidney. One has no reason to regret the performance of retrograde pyelographic examination in these cases, and in several instances more precise information regarding the condition of the kidney has been obtained than was possible by excretory urographic studies. Too many general physicians rely on the erroneous information often obtained from the latter. However, many such injuries can be diagnosed by excretory urographic studies alone. One should not hesitate to take a retrograde pyelogram in any instance in which the diagnosis and extent of the injury are in doubt or in which the kidney or the renal pelvis is not well outlined by an excretory urogram. A true rupture of the kidney, resulting in gross injury to the pelvis, cortex or capsule represents serious renal damage. The patient should be operated on as soon as the diagnosis is made, provided shock and other injuries will permit. To postpone surgical intervention in the presence of an operable lesion is poor surgical judgment. The literature contains accounts of many such lesions treated conservatively too long, with a subsequent loss of the kidney or even of life. Surgical intervention, if performed early, may preserve a severely damaged kidney. The degree of shock, however, must first be determined, and treatment must be instituted for the control of shock before surgical operation is begun. The most conservative treatment is (a) prompt exposure of the kidney, (b) repair when possible or (c) early nephrectomy. When doubt persists concerning the extent of the renal injury after all available diagnostic procedures have been done, an early exploratory operation is preferable to prolonged expectant treatment.

Cahill¹⁴ stated that renal injuries vary and that they may be only a minor portion of a profound injury. With a penetrating wound of the abdomen the kidney is often not a major part of the picture but is obscured by intestinal or other injuries. In the late war the infrequency

13. Henline, R. B., in discussion on Sargent.¹²

14. Cahill, G. F., in discussion on Sargent.¹²

of renal injury was due to the fact that most of those seriously wounded died on the field. When the kidney is the major site of trauma, there may be many sources. The symptom most frequently seen is hematuria. Cahill sees no objection to the use of an intravenous urogram in such cases. If the patient is in shock, naturally that condition should be relieved by transfusion and other therapeutic aid and the intravenous urogram taken subsequently. The secretion from the uninjured kidney shows that it is present. The injured kidney may or may not secrete. If it secretes well, the injury is probably not severe and expectant treatment is in order. If the kidney does not secrete and an increasing hematoma is present in the flank, then, operation being contemplated, a retrograde pyelogram may be done.

Stirling¹⁵ stated that, in his experience, in the majority of the cases diagnosis of injuries of the kidney can be made by intravenous pyelographic study. He reviewed 34 recent cases in which there was a positive diagnosis in 23, and in only 7 instances was it necessary to take a retrograde pyelogram. He expressed the belief that instrumental pyelographic procedures should be reserved solely for cases in which bleeding continues, with unsatisfactory pyelograms. In the presence of severe contusions the first intravenous pyelogram may be unsatisfactory, whereas if another is taken in from twenty-four to forty-eight hours it frequently will show a good shadow. In a majority of the cases the lesions reported as ruptures of the kidney are only contusions and respond to conservative measures. Stirling's experimental work and clinical studies indicate that in the presence of severe injury to the kidney operative intervention is more likely to give a good result than is the conservative method. Severe injuries of the kidney produce marked vascular damage, which may later cause ischemia of the kidney followed by hypertension. Patients who have renal injuries should be watched for evidence of hypertension. The loss of blood in renal injuries makes anemia an important factor during convalescence. This complication is due not to the simple loss of blood but to the liberation by the injured kidney of some substance capable of causing toxic destruction of red blood cells.

In 3 instances in O'Connor's¹⁶ experience in which a more or less minor injury of the kidney, at least from a clinical point of view at the time of the injury, apparently responded successfully to palliative treatment the patients (against orders) went back to an active life, and all 3 of them returned with massive hemorrhage coming on as long as four weeks after their discharge from the hospital, which necessitated surgical intervention. One of these patients, who had a massive hemorrhage

15. Stirling, W. C., in discussion on Sargent.¹²

16. O'Connor, V. J., in discussion on Sargent.¹²

which lasted only twenty-four hours, responded quickly to four or five days of rest in bed, left the hospital against orders on the tenth day and returned three and a half weeks later with a kidney which was completely broken in two as the result of lifting a heavy suitcase. Two boys with football injuries were allowed to return to active life. Both resumed playing football within three weeks, and both returned with massive hemorrhage which necessitated surgical intervention. O'Connor expressed the belief that patients who are treated palliatively should be kept at rest at least for two weeks and that their physical activity should be limited for a minimal period of four to eight weeks.

Aneurysm of the Renal Artery.—Aneurysm of the renal artery is rare. Howard, Suby and Harberson¹⁷ gave a résumé of the subject and reported 1 case of false aneurysm and 2 cases of true aneurysm of the renal artery.

Trauma seems to be the most important single cause of aneurysm of the renal artery. Of the 65 cases reported in the medical literature, in 24 there was a definite history of trauma, varying from that received in a very slight fall to a severe crushing injury. The extent of the damage to the renal vessel may be so great that an aneurysm is formed immediately, or it may be slight, with only a weakness produced in the vessel wall, so that the aneurysm may develop slowly over a period of months. Aside from trauma, severe infection seems to be the most important cause of renal aneurysm. Diseases of the arterial wall itself are statistically the third most important cause of renal aneurysm.

The pathologic development of aneurysm of the renal artery is essentially the same as that of any other aneurysm. An aneurysm may be either true or false. By definition a true aneurysm is one whose sac is formed by the arterial wall, one part of which, at least, must be intact. A false aneurysm, on the other hand, is one which follows trauma with rupture of all the coats of the artery and retention of blood by the surrounding tissue. A true aneurysm is usually the result of fatty degeneration, sclerosis, inflammatory changes or degeneration of the elastic fibers of the blood vessel wall. False aneurysms of the renal artery are usually much larger than true aneurysms and as a rule contain laminated blood clot.

A patient may have no symptoms and still have an aneurysm of the renal artery. In cases of the recognized condition, however, those in which the aneurysms ruptured or are relatively large, pain is the most common symptom. With a ruptured aneurysm the pain may be sharp and excruciating, and it is often accompanied with the symptoms and signs of profound shock. The patient who has a large unruptured

17. Howard, H. H.; Suby, H. I., and Harberson, J. C.: *Aneurysm of the Renal Artery*, J. Urol. 45:41-54 (Jan.) 1941.

or quiescent false aneurysm may complain of a dull ache in the renal region or may have attacks of renal colic.

Immediate surgical intervention, with nephrectomy as the operation of choice, should be done in all cases of aneurysm of the renal artery. Of the 24 patients who were operated on, only 5 died, a mortality rate of 21 per cent. Three of these operative deaths occurred in cases in which either incision and drainage or partial incision of the sac, not nephrectomy, was done. Subsequent hemorrhage was the cause of death. All of the patients who were not operated on died.

URETER

Anomaly.—Harrill¹⁸ reported a case of hydronephrosis produced by obstruction to a ureter which passed around the right branch of a double vena cava. This was the fifth such case in the literature. After the lower portion of the pelvis had been cut across, the ureter was drawn from behind the right vena cava, placed in the normal position and anastomosed at the point of division. This case is the only one of the kind in which the division and the anastomosis were above the uretero-pelvic juncture.

Tumor.—Cook and Counsellor¹⁹ stated that, although primary epithelioma of the ureter is a comparatively rare disease, its incidence is sufficient to make it a possible cause of hydronephrosis, especially if it is associated with hematuria. Hematuria is the outstanding symptom, and the blood in the urine is often bright red.

Excretory urograms are valuable if the kidney is still functioning, in that they reveal the extent of the pyelectasis, caliectasis and ureterectasis present, but they may or may not identify the obstructing lesion of the ureter. Retrograde pyelograms are essential to demonstrate the lesion in most instances and should be made whenever a patient with hydronephrosis is of the "cancer age" if the cause is not definitely understood.

Treatment of the condition is surgical, and surgical intervention should be instituted early. Complete extirpation of the kidney, the ureter and the ureterovesical segment of the bladder should be done because of the tendency for the growth to extend through the wall of the ureter to adjacent structures, and all periureteral adipose tissue should be removed with the ureter.

The results of surgical treatment parallel closely the completeness of the operation, the degree of malignancy present and the operability of

18. Harrill, H. C.: Rectocaval Ureter: Report of a Case with Operative Correction of the Defect, *J. Urol.* **44**:450-457 (Oct.) 1940.

19. Cook, E. N., and Counsellor, V. S.: Primary Epithelioma of the Ureter, *J. A. M. A.* **116**:122-126 (Jan 11) 1941.

the lesion. Large lesions of low malignancy may be as great a hazard to the life of the patient as small, highly malignant lesions. Roentgen therapy should be administered postoperatively to all patients.

Injury.—Hepler²⁰ discussed injuries to the ureter which occur accidentally in the course of pelvic operations and therefore are primarily the problem of the general surgeon. Seven hundred and seventy-six such injuries were reported; 659 patients suffered injuries to one ureter, and 117, to both ureters. Hepler added 6 cases, in 5 of which injury was unilateral and in 1 of which it was bilateral. These figures do not represent the frequency with which these injuries occur, because many are unrecognized and some are not reported.

There is lack of uniformity of opinion as to the best methods of treatment, because the numerous contingencies do not permit a categorical plan of management. Certain principles, however, can be laid down, based on the time element, the type and extent of injury and the condition of the patient. When the injury is recognized immediately the problem is largely surgical, but when it is not discovered until after the operation it becomes strictly urologic because of the complications of infection, obstruction and functional damage.

The types of injury, in order of their frequency are those due to ligation, those due to clamping, those due to incision (partial or complete) and those due to resection. Clamping usually destroys the vitality of the crushed segment and is followed by necrosis, so that the badly crushed ureter should be treated as if it were severed. When the injury is discovered during the operation, the ideal procedure for the badly crushed or severed ureter is an end to end anastomosis over an indwelling ureteral catheter. The most important step in this procedure is deviation of the urine by another catheter, inserted in a slit in the ureter well above the line of suture and brought out through the flank. Both catheters are removed in a week. If the injury is near the bladder, a ureteroureteral anastomosis may not be possible, and it may become necessary to implant the proximal end into the bladder.

If a fairly large segment of the ureter has been excised, neither ureteroureterostomy nor ureterocystostomy is feasible, because of the gap in ureteral continuity. The procedures in such a situation, in the order of frequency with which they are recommended in the literature, are: (1) ligation of the proximal end of the ureter and replacement of it; (2) nephrectomy; (3) implantation into the skin (dermatoureterostomy), and (4) implantation into the bowel (ureteroenterostomy).

Hepler expressed the opinion that this order is inverse to the desirability of the operations. The procedure which most frequently is

20. Hepler, A. B.: Management of Surgical Injuries to the Ureter. *West. J. Surg.* 48:486-492 (Aug.) 1940.

recommended, to ligate the proximal end of the ureter and drop it back, is not surgical. First, the condition of the other kidney is not known as a rule, and under these circumstances it is unwise to destroy the function of one kidney. Palpation of the opposite kidney gives no information as to its function. Second, ligation of the ureter is followed by hydronephrosis in the great majority of instances and not by primary renal atrophy as is often assumed. Third, this procedure may be an easy way out of the difficulty, but it is not a safe one. Three per cent of the patients will die, 15 per cent will require early nephrectomy for infection, and 24 per cent will have fistulas subsequently.

Immediate nephrectomy will obviate these complications, but the addition of a second major operation, which sacrifices a good kidney, seems a cumbersome way out of the difficulty when a simpler procedure, ureterointestinal implantation, gives a reasonable assurance of renal conservation.

Conservative surgeons may temporize by transplanting the proximal end of the ureter into the skin, but obstruction and infection are so common that delayed anastomoses are difficult and unsatisfactory, and nephrectomy is usually inevitable.

When there is more general recognition of its simplicity and of the absence of postoperative morbidity, ureterointestinal implantation will be decidedly preferred to the other methods of disposal of the injured ureter when a portion of it has been excised.

The management becomes more complicated when the injuries are not recognized until after operation. The symptoms may be interpreted as infection, peritonitis or intestinal obstruction until leakage of urine through the wound or the vagina makes the condition evident. If the ureter has been ligated, hydronephrosis may develop and be unnoticed until months later or until the kidney becomes infected.

If unilateral injuries are recognized soon after operation there are three indications for intervention: (1) drainage of accumulated urine in the flank or pelvis; (2) high lumbar ureterostomy or nephrectomy, if the ureter has been ligated, to provide drainage until it is determined whether or not the suture will absorb, and (3) if a fistula has been established, the use of an indwelling ureteral catheter.

With these exceptions there is no need for haste. Some fistulas will close spontaneously, although too often the so-called spontaneous cure is the result of cessation of function of the corresponding kidney. In the presence of a sound kidney on the opposite side, nephrectomy is the quickest and safest way to relieve the patient of his difficulty. Conservative surgical procedure is apt to fail, because anastomosis of ureters which have been obstructed and infected is an entirely different matter from anastomosis of normal ureters at the time of injury. However, if

the opposite kidney is not sound, some form of anastomosis is necessary—ureteroureteral, ureterovesical or ureterointestinal.

The necessity for immediate treatment in the presence of bilateral ligation is obvious. Reopening the abdomen in an attempt at deligation is to be condemned. The anatomic distortion, the extensive exudate and the inevitable bleeding make this procedure extremely difficult and dangerous for a patient already desperately ill. In a reported series of 13 cases of bilateral ligation of the ureter, immediate laparotomy and deligation were done in 8. Seven of the patients died, and the other later required nephrectomy.

The operation of choice is bilateral high lumbar ureterostomy with the insertion of soft rubber catheters into the pelvis for drainage until it is definitely determined that the ligation will not reabsorb and that the ureteral lumen will not be reestablished. It is then necessary to make some form of ureteral anastomosis. The technical difficulties are increased by the changes in the ureters, which are usually dilated, infiltrated and buried in scar tissue behind thickened peritoneum in a pelvis filled with adhesions. Of the methods of disposal, transplantation to the bowel is the best.

Rusche and Bacon²¹ stated that intraureteral instrumentation as a cause of ureteral injury is dependent usually on impaction of a calculus and adjacent disease of the ureter. They expressed the opinion that the present increase in incidence of ureteral perforation is related closely to the recent development of many devices designed to remove calculi. The treatment of a perforated ureter is usually incision and drainage of the extravasated urine and removal of the calculus. Rusche and Bacon reported 14 cases of ureteral injury and 2 cases of foreign body in the ureter in which the lesions and the foreign bodies were due to use of the cystoscope.

Swan²² considered injuries of the kidneys under three headings: (1) subparietal injuries with no open wound communicating with the exterior; (2) incised and punctured wounds, and (3) gunshot wounds.

Only injuries in the first group are discussed here. These constitute by far the largest group of renal injuries, and the diagnosis is generally easy. The history of injury from a crush followed immediately by pain in the side, collapse and shock, the palpation of a tumor in the lumbar region and the presence of blood in the first specimen of urine passed after the accident usually point to the diagnosis. In cases in which

21. Rusche, C. F., and Bacon, S. K.: *Injury of the Ureter Due to Cystoscopic Intraureteral Instrumentation: Report of Sixteen Cases*, *J. Urol.* **44**:777-793 (Dec.) 1940.

22. Swan, R. H. J.: *Injuries of the Kidney*, *Brit. J. Urol.* **12**:161-176 (Sept.) 1940.

hematuria is absent the diagnosis can be made on the nature of the accident, the rigidity of the abdominal muscles on the affected side, the presence of a tumor in the lumbar region and the degree of shock. Frequently there is associated rupture of the spleen; in such circumstances surgical treatment should be addressed first to the spleen as the organ less able to suffer delay in treatment.

In a general way it is easier to make a diagnosis of trauma to a kidney than to foretell the amount of damage the organ has sustained. The extent of the perinephric swelling points to the severity of the lesion, but palpation of the mass may be difficult, for the swelling may be masked by the muscular rigidity or the abdominal distention.

The primary treatment consists of rest, warmth and measures to combat the shock. When hemorrhage is still going on, a progressive increase in the pulse rate, increasing anemia and a coincident fall in the blood pressure form important indications for operative intervention. Many patients are too acutely ill to undergo instrumental and roentgen examination, and, in addition, the evidence obtained by these diagnostic aids is often too uncertain to be of great value. An intravenous pyelogram is of use, however, in revealing the presence of a functioning kidney on the other side. Ascending pyelograms may show a more definite shadow, but there remains the risk of injecting the solution into the perinephric effusion or of starting further bleeding.

The actual operation carried out on the kidney must necessarily first be an exploration, and it must be left to the surgeon's judgment to deal with the condition he finds. It should be his constant aim to preserve the kidney if there is any possibility of doing so, and it has been shown that functional recovery is possible after the repair of lacerations at the expense of cicatrizations in the area of injury. Frequently a laceration of the cortical area, even one implicating the calices, may be closed by mattress sutures or by incorporating a piece of muscle or fat in the line of suture to strengthen it. In many cases in which the renal vessels are torn or in which the pelvis is extensively lacerated, nephrectomy must be performed as a life-saving measure. Until the renal pedicle can be controlled, difficulties may arise during the operation from the amount of blood constantly welling up from the depth of the wound, and hemorrhage may be started anew by the manipulations necessary to expose the kidney. Provisions for an immediate transfusion at the close of operation should always be made.

In some cases operation may become necessary at a later stage on account of recurrent bleeding or on account of infection in the area of subcapsular laceration forming localized abscess or pyonephrosis. Infection is more likely to arise, however, in a perinephric effusion (in about 10 per cent of cases) at varying intervals after a renal laceration. It is

evidenced by increase of lumbar pain and tenderness, progressive leukocytosis and irregular pyrexia with pallor and sweating. Later results that may call for operative treatment are those due to contracting scar tissue, which may cause dilatation of one or more calices, or to such cicatrizations about the ureter as give rise to definite hydronephrosis.

Stenosis.—Jewett,²³ from a study of 71 cases of hydronephrosis, established three fundamental causes of obstruction at the upper end of the ureter: bands and kinks, in 4 cases (5.6 per cent); accessory renal vessels, in 24 cases (33.8 per cent), and stenosis, in 43 cases (60.5 per cent). In the group of cases in which stenosis was the underlying cause of obstruction, secondary accelerating factors were accessory renal vessels, infection, kink and fixation, high ureteral insertion and, possibly, rapid renal growth during puberty.

In the majority of normal persons there is no line of demarcation between the renal pelvis and the ureter. Any deviation from the normal funnel-shaped pyeloureteral outlet is probably pathologic. Moderate deviation, sufficient to cause only minimal obstruction, can be compensated for by work hypertrophy of the pelvic musculature.

When the ureter is normal, a sharply defined and permanently persistent ureteropelvic juncture in the presence of pyelectasis should be considered obstructive.

Lymph Channels.—Parker,²⁴ after making more than one hundred separate injections into various portions of the walls of ureters, stated that no complete network of lymphatic channels can be demonstrated throughout the walls of ureters by means of Gerota's injection mass. The lymphatic capillaries in the walls of the ureters give rise to lymph collectors which pass diagonally outward, through the musculature of the ureters.

These lymph collectors course in the adventitial coverings of the ureters. They may pass upward and downward from the point of injection for greater or lesser distances. Eventually they always leave the renal ducts to pass to regional lymph nodes.

The regional lymph nodes of the ureters belong to the lateral abdominal lymphatic chains, the common iliac, the external iliac and the hypogastric groups of nodes. Lymph nodules located along the lymph collectors from the kidney receive lymph vessels directly from the pelves of the kidneys. Except for these, no lymph nodes separate from the main

23. Jewett, H. J.: *Stenosis of the Ureteropelvic Juncture: Congenital and Acquired*, J. Urol. **44**:247-258 (Sept.) 1940.

24. Parker, A. E.: *Lymph Collectors from the Ureters, Their Regional Nodes and Relations to Posterior Abdominal Lymph Channels*, J. Urol. **43**:811-830 (June) 1940.

posterior abdominal and pelvic lymph nodes were found to act as regional nodes for lymph collectors from the renal ducts.

Transplantation.—Hepler²⁵ reported on the end results of uretero-intestinal implantation. The operation of vesical exclusion by transplantation of the ureter to the sigmoid or to the rectum was performed in 27 cases, with 2 deaths, a mortality rate of 7.4 per cent.

When the operation is done for the congenital deformities seen in children, such as exstrophy and epispadias without a vesical sphincter, the results, both immediate and late, are excellent. There were 16 patients in this group, with no postoperative deaths. All of the children except 2 are living and well.

When ureterointestinal implantation is done for the acquired lesions of adults, such as carcinoma of the bladder, intractable tuberculous or interstitial cystitis or inoperable fistula, the damage to the upper part of the urinary tract secondary to these conditions adds to the operative risk and modifies the functional results. There were 11 cases in this group, with 2 postoperative deaths, a mortality rate of 18.3 per cent. There were 4 late deaths, all but 1 of which were from extension of the primary disease and could not be attributed to the ureteroenterostomy. The use of this operation earlier than it ordinarily is employed would make it a truly conservative procedure and not a last desperate means to relieve intolerable symptoms of vesical disease.

One of the chief considerations in bringing about a successful outcome is to avoid obstruction of the ureter at the site of the anastomosis, and to this end the simple methods, which avoid a too tight fixation of the ureter in the submucosal gutter, seem to be the best. Many of the elaborate methods devised to avoid complications seem only to invite them.

In the presence of lesions of the upper portion of the urinary tract the diseased and abnormal ureters add to the technical difficulties and increase the risk of implantation. However, in some situations in which relief is imperative one should not be too easily sidetracked from a contemplated ureteroenterostomy by the dogma that abnormal or dilated ureters should never be transplanted. It is surprising at times what good results are obtained under adverse circumstances.

BLADDER

Diverticulum—In a review of his 236 cases of diverticulum of the bladder, Kretschmer²⁶ noted that obstruction at the vesical outlet was

25. Hepler, A. B.: The End Results of Uretero-Intestinal Implantation, *J. Urol.* **41**:794-807 (Dec.) 1940.

26. Kretschmer, H. I.: Diverticula of the Urinary Bladder, *Surg., Gynec. & Obst.* **71**:491-503 (Oct.) 1940.

present in all (230) in which data were available (100 per cent). Benign prostatic hypertrophy was present in 153 cases (66.52 per cent), median bar in 34 (14.78 per cent), contracted internal urethral orifice in 18 (7.39 per cent), stricture of the urethra in 5 (2.19 per cent) and congenital valves of the posterior urethra in 3 (1.30 per cent).

Diverticula are rare in women and in children. Eighty-seven per cent occur in the age period after 50 years, a time when obstruction at the vesical neck is common. Seven of the patients in Kretschmer's series were women; in 4 of these the diverticulum was associated with contraction of the vesical outlet, and in 3, with extensive carcinoma of the bladder.

Diverticula may be single or multiple. The incidence in the cases in this series was: single, 137, and multiple, 99. They may vary widely in size, from those with a capacity of a few cubic centimeters to those holding several liters. Some may empty with the contraction of the bladder; others do not and are known as "retention diverticula." This point may be determined by cystograms taken after injection of a contrast medium.

Infection, or diverticulitis, is the most common complication. Once started, it is difficult to treat and leads to peridiverticulitis with adhesions to surrounding structures.

Primary carcinoma arising in a diverticulum is a rare complication. It occurred 4 times in this series. Such a tumor must be distinguished from one which arises in the bladder and invades the diverticulum secondarily.

It is not surprising that stones should occasionally be found in diverticula, because two conditions that predispose to calculosis, namely, retention of urine and infection frequently are present. Stones in diverticula were found in 8 of Kretschmer's cases. Tuberculosis and leukoplakia are rare complications, but they have been reported.

There are no symptoms pathognomonic of diverticulum. The clinical picture is that of obstruction of the vesical neck, and it is usually during the investigation of this condition that the diverticulum is found. Routine cystographic procedures often will reveal the presence of a diverticulum when it is least expected. Lateral as well as anteroposterior films should be made. Contrast cystograms are of value, especially in determining whether the diverticulum empties.

The treatment consists first in removal of the obstruction at the vesical outlet. Whether or not diverticulectomy is performed depends on the size of the diverticulum, its ability to drain and the persistence of residual urine or of infection with dysuria. Kretschmer stated that he does not remove a small diverticulum if the removal of the obstruction relieves the infection and the subjective symptoms. The same rule applies to a

larger diverticulum unless it is close to or impinges on a ureter and produces ureteral obstruction. Under these circumstances Kretschmer removes the large diverticulum first and then disposes of the obstruction of the vesical neck.

De Illyés²⁷ reported his technic, used for the last twenty years in the University Clinic of Urology in Budapest, Hungary, in surgical treatment of diverticulum of the bladder. A high incision is made into the bladder, the pouch is irrigated, and a long metal instrument resembling an elevator is passed into the pouch. With the sides of the incision held tense by forceps, the wall of the bladder on the side of the diverticulum is freed, mostly by blunt but in part by sharp dissection. It is usually necessary to open the peritoneum horizontally if exposure of the top wall of the bladder is desired. Exposure of the bladder requires the ligation of only a few blood vessels. The wall is cut with straight scissors all the way to the opening of the diverticulum. The opening of the pouch then is eneirole with an incision through the entire thickness of the wall. The surgeon proceeding with caution, a layer is reached that separates easily, and the diverticulum can be readily isolated from the bladder. The extremity of the metal instrument, previously passed into the pouch, can be easily felt, and it serves as a guide to the depth of the pouch. This method also facilitates the locating or saving of the neighboring ureter or vas deferens. Furthermore, it enables the surgeon to ascertain whether or not the fundus is separable from the rectum; when the fundus cannot be freed it is wise to make a circular incision around the adhering part to avoid injury to the rectum. This part is left intact, and only the infected mucous membrane is removed.

Since the infected bladder and diverticulum unavoidably come into contact with the edges of the incision, arrangements must be made for drainage. Iodoform gauze tampons having proved inefficient, Illyés has devised a special method of drainage, as follows: Feeling for the lower edge of the os pubis, at a point about 1 or 2 fingerbreadths to one side from the middle of the symphysis, he punctures the soft parts with a blunt forceps; then, feeling the end of the instrument through the perineum, he performs an incision in the skin the size of a buttonhole, through which he thrusts the instrument. A suitable drainage tube is applied and drawn into the wound behind the bladder by means of the instrument. This method of drainage has been of great help in numerous cases. When there is no longer the need for draining, the tube can be taken out; the channel (3 to 4 mm. in diameter) left by it contracts within a few days and closes without leaving the slightest trace.

27. de Illyés, G.: The Surgical Treatment of Diverticula of the Bladder, *Brit. J. Urol.* **12**:104-120 (June) 1940.

This operative method undoubtedly is not perfect, but it is palliative when a radical operation is contraindicated. In cases of older patients who have prostatic hypertrophy and difficulty in emptying the bladder, such diverticula are often present. These patients are already suffering from infection when seen, because urinary obstructions have been treated by catheterization. In such cases Illyés made it a practice first to perform prostatectomy and then to extirpate the diverticulum all in one sitting, as a simpler and more sparing procedure for the patient. At the time of this report he had used this method in 25 cases; in 20 of these healing took place and the patients were healthy. In 11 cases he had performed implantation of the ureter after excision of the diverticulum. In the 168 cases of diverticulum which he had handled, 166 of the patients were men and 2 were women. In the cases of 59 men his treatment was surgical. Illyés expressed his conviction that the diverticulum must be treated surgically, as the only way in which certain and lasting healing can be obtained. The operation is done under sacral anesthesia and local infiltration. All tearing, jerking, undue torsion and rough retraction are forbidden. If this rule is followed, the patient is spared a great deal of pain. Illyés attributed much of his success with serious and complicated conditions to the employment of perineal drainage. He had not seen a single gross infection develop.

Vesicoappendical Fistula.—Pemberton, Pool and Miller²⁸ considered the rare condition of vesicoappendical fistula and described 3 cases.

They had observed that there usually is a history of distress, perhaps acute, in one of the lower abdominal quadrants. Simultaneously with this distress, burning and frequency of urination occur. Symptoms referable to the urinary bladder alone may be the presenting complaint. From the diagnostic standpoint a history of passage of gas and feces through the urethra is pathognomonic of a vesicoenteric fistula. Cystoscopic examination reveals the opening usually present on the right side of the bladder. Frequently the aperture may not be seen, for a mass of granulation tissue or a depressed necrotic region in the bladder may be the only evidence that a fistula exists. When suspicion exists that a fistulous tract is present, a lead catheter may be passed gently through the aperture and a substance opaque to the roentgen rays may be injected. Cystograms may be of value, in that the medium may outline the abnormal tract.

Pemberton, Pool and Miller reported that 5 patients with vesicoappendical fistulas had been examined and treated at the Mayo Clinic. Two of the cases had been reported elsewhere by Rankin and Judd.

28. Pemberton, J. deJ.; Pool, T. L., and Miller, J. M.: *Vesico-Appendical Fistulas*, J. Urol. 44:274-278 (Sept.) 1940.

Three men and 2 women ranging in age from 30 to 54 years comprised the group of patients. Definite acute appendicitis was present in 3 cases. In another case the history was suggestive of acute appendicitis, while the patient in the fifth case gave no such history. Pyuria was present in all the cases. Cystoscopic examinations in 3 cases revealed diffuse inflammatory changes in 2, with the same changes present in the left base of the bladder in 1. In the 2 other cases the observations were limited to the right base of the bladder. In 2 cases cystograms were made; one cystogram did not disclose any abnormality, but the other revealed a sacculated bladder. In 2 cases excretory urographic study did not reveal abnormalities.

The 3 patients newly reported on all underwent surgical operation (appendectomy and closure of the opening into the bladder). Of these 3, 1 succumbed to generalized peritonitis.

The authors recommended culture of the urine and institution of appropriate chemotherapy.

Obstruction of Vesical Neck.—Young²⁹ stated that chronic inflammatory conditions in the female urethra, especially in the deep portions and at the vesical neck, are common in women. They are accompanied with symptoms that often are referred to regions higher in the urinary tract. In most cases, however, local symptoms are present in the urethra and in the bladder. Chronic inflammatory changes in the mucous membrane, in periurethral structures and particularly in the glands are often present and evinced by swelling, by edema, by cystic and polypoid formations and sometimes by the development of definite bars or contractures of the vesical orifice. For the proper study of these changes an antegrade or fore-oblique telescope or urethroscope is essential. These lesions may often be missed during cystoscopic examination with the right angle telescope. The conditions which produce such severe local and referred symptoms are readily cured by endourethral treatment: applications of silver nitrate fulguration, the punch operation or excision of the obstructing bar. Severely inflamed regions may be treated either with the simple punch instrument or with the electrical resectoscope. Care must be taken not to overdo, lest temporary incontinence occur. Accurate and adequate endoscopic methods often clear up long-standing and troublesome conditions.

Rupture.—Peacock³⁰ reported a series of 28 cases of rupture of the bladder. The ages of the patients varied from 11 to 70 years, the average being 34 years. Eighteen patients were males and 10 were females.

29. Young, H. H.: The Pathology and Treatment of Obstructions at the Vesical Neck in Women, *J. A. M. A.* **115**:2133-2135 (Dec. 21) 1940.

30. Peacock, A. H.: Rupture of the Urinary Bladder, *Northwest Med.* **39**:248-252 (July) 1940.

Hazardous occupations, such as logging, railroading, electric work and stevedoring, increase the incidence of rupture of the bladder in men and boys. Loggers comprise 25 per cent of the patients; students, 25 per cent; housewives, riding as automobile passengers, 14 per cent, and laborers, 11 per cent.

The most frequent cause of rupture of the bladder was fracture of the bony pelvis. In 85 per cent of the cases reported by Peacock such fractures were present.

Fifty per cent of ruptures of the bladder were due to motor vehicle collisions and accidents. The average interval between the accident and surgical treatment was eleven hours. Few patients who were allowed to go without operation for several days escaped disastrous consequences. Four deaths occurred in the series.

The commonest complications were pyelonephrosis, perineal abscess from hematoma, peritonitis, osteomyelitis, laceration of the kidney, rupture of the rectum and vesical calculus. The long-standing drainage of the bladder, the infection and the decubitus position are all contributory to slow convalescence.

PROSTATE GLAND

Hypertrophy.—Henline³¹ described a method of subtotal perineal prostatectomy. The pathologic changes of prostatic disease frequently are overlooked in selecting the surgical procedure for relief of symptoms. Each of the three main prostatic procedures has its place, and no one method should be used to the exclusion of the others. Infection of the remnants of the functioning prostatic gland, prostatic calculi and early malignant disease, particularly in the posterior lobe of the gland, may be completely removed only by the perineal approach. Patients should be warned of the frequent occurrence of impotence following subtotal perineal prostatectomy. Recent improvements in surgical technic and mastery of procedure should dispel the fear of urinary incontinence or fecal fistula.

Emmett³² considered the preoperative and postoperative care of patients on whom transurethral prostatectomy is performed. According to him, preoperative care begins with the first visit of the physician when he is called to relieve the patient of retained urine. The important factors to be kept in mind during instrumentation are: that the vesical mucosa has been traumatized by stretching, which makes it more susceptible to infection; that urinary retention of long standing produces

31. Henline, R. B.: Prostatic Disease, with Special Reference to the Various Causes and Types as Well as Their Treatment, *South. Surgeon* 9:360-368 (May) 1940.

32. Emmett, J. L.: Preoperative and Postoperative Care in Transurethral Prostatectomy, *S. Clin. North America* 20:1061-1075 (Aug.) 1940.

stasis and renal insufficiency; that instrumentation may cause exacerbation of an infection already present, and that the physician is dealing with patients of advanced age, whose resistance to any disease is lower than that of younger persons.

The difficulties of catheterization are easily understood when one realizes that at times there is difficulty in catheterizing a normal male urethra. Furthermore, a "pocketed" posterior urethra may add difficulty. Time should always be taken to sterilize catheters properly, and time should also be taken to prepare the patient with opiates prior to catheterization so that he will not be tense and irritable.

The technic of catheterization is as follows: Proceed gently and slowly, using a plain soft rubber catheter. If this instrument cannot be passed, use one with a coude tip. If this fails, try a filiform followed by a Phillips catheter or a semirigid woven catheter with a coude or a bicoude curve. Metal catheters are best avoided, as they may cause more harm than good.

If catheterization is extremely difficult, there are several other procedures that may be tried. Usually after needle aspiration of the urine the catheter may be passed easily. The patient may be hospitalized and anesthetized before catheterization is attempted. Finally, suprapubic cystostomy may be necessary.

Aside from the patient's discomfort from acute urinary retention, the only indication for preoperative drainage of the urinary tract is renal insufficiency. This is in direct contrast to former teaching, which held that preliminary drainage was essential in order to "vaccinate" the patient against his infection. However, infection is an important factor in preliminary drainage, and Emmett pointed out that infection produced by the indwelling catheter is due to poor technic and uncleanness. The institution of prolonged drainage should begin by introduction of a carefully sterilized catheter with rigid aseptic precautions. The catheter should be carefully adjusted and fastened in place. A self-retaining catheter may be used, but in either event the catheter should be connected to a closed system of drainage. To reduce the incidence of ascending infection, the drainage bottle should be boiled before being replaced after removal for emptying. It is extremely important that the catheter be adjusted immediately if it becomes painful or if the patient voids around it. Unless this is done, chills and fever will result. It is essential that the strips of adhesive tape used to fasten the catheter be placed so that they do not occlude the urethral meatus and prevent free drainage of the secretions of the urethra.

The only indication for preliminary drainage is a retention of urea in the blood, and if the value for blood urea is more than 50 or 60 mg. per hundred cubic centimeters urethral drainage should be employed. However, this is a variable factor; for instance, in the event that the

concentration of urea is 200 or 300 mg. per hundred cubic centimeters and the urinary output is good (2 or 3 liters daily) while the patient is being prepared, it is considered safe to proceed when the concentration of urea is about 150 mg. per hundred cubic centimeters, for in some cases it may become fixed at a high level. Furthermore, the danger from infection is great enough so that it is felt best to proceed with transurethral resection. Suprapubic drainage is rarely indicated, according to Emmett, for the purpose of preliminary drainage, this procedure being employed in only about 6 cases a year, during which time 1,000 prostatic resections are performed.

Concerning the administration of fluids in cases of renal insufficiency, it is best not to exceed 3,000 cc. daily, and care should be taken not to give too much salt. The associated diseases of which one should be aware are cardiac disease, hypertension, arteriosclerosis, diabetes and senile dementia, as these complicate the management of patients with prostatic obstruction.

The question of the preoperative use of urinary antiseptics is usually not considered unless the urine is very foul, in which case vesical lavage and antiseptics are used. Usually it is best to proceed with resection as soon as possible. Blood transfusions are not given unless the concentration of hemoglobin is less than 10 Gm. per hundred cubic centimeters of blood. Emmett expressed the belief that transfusion is more beneficial after resection.

The postoperative care was summed up under three headings: (1) hemostasis, (2) adequate drainage and (3) prevention and eradication of infection. At the conclusion of resection the usual custom is to insert a no. 22 F. soft rubber urethral catheter, but if there is considerable oozing a hemostatic catheter bag is used and appropriate tension is made by traction. The most important factor in the control of bleeding is irrigation of the bladder. This should be done as often as every twenty or thirty minutes for the first hour or two after operation. In most cases the urine is clear after eighteen to twenty-four hours. Immediately after resection, the important precautions to prevent further hemorrhage are to drain the bladder well and keep the patient quiet. In the event that hemorrhage does occur after resection, it is necessary to evacuate the clots from the bladder, and if doubt exists it is best to reexamine the vesical neck for the presence of bleeding vessels. Blood transfusions should be used, as most deaths from renal insufficiency, oliguria and cardiac failure are due to excessive loss of blood.

Fluids are given postoperatively as follows: From 1,000 to 1,500 cc. of physiologic solution of sodium chloride or a 5 per cent solution of dextrose is given intravenously immediately after the operation. fluids and food are given by mouth on the afternoon of the day of operation.

The catheter is usually left in place for forty-eight or seventy-two hours after resection. If the patient voids well after the catheter is removed, it is not reinserted until the patient has left the hospital; about the tenth day, during a visit to the office, a catheter is passed, and if there is no residual urine the patient is dismissed on the twelfth or fourteenth day after operation. If subsequently the patient experiences any difficulty in voiding, the catheter is reintroduced after about six hours. If there is any residual urine, the catheter is left in for forty-eight hours. If residual urine persists it is best to plan another cystoscopic examination, but this should not be done until seven or eight days after the first operation.

Febrile reactions after a cold punch operation most commonly are due to: (1) infection in the prostatic bed, (2) acute pyelonephritis and (3) septicemia. Administration of mercurochrome intravenously, 5 to 10 cc. of 1 per cent solution in 500 cc. of physiologic solution of sodium chloride, may be a life-saving procedure. When definite septicemia is present, sulfanilamide or one of its derivatives is most efficacious. In the uncomplicated case, the patient is allowed to be up in a chair the day after operation.

Acute epididymitis subsequent to resection is becoming rare, since resections are being done more completely. Postoperative urethral stricture is becoming less common, since surgeons are resorting to perineal transurethral resection when the urethra is too small to admit the resectoscope comfortably. Occasionally a periurethral abscess is encountered; such an abscess should be incised as soon as the diagnosis is made. Postoperative pneumonia is treated in the usual manner. Fortunately perforation of the bladder is becoming rare, since surgeons have become better trained in the technic of transurethral resection. However, if this complication is suspected, suprapubic drainage should be carried out if there are signs of extension or extravasation.

Transurethral Resection.—Kretschmer³³ discussed the present trend of transurethral resection. He stated that shortly after the inauguration of resection the operation was severely criticized because of some of the bad results which followed its use. The method was criticized without taking into consideration the man who sat at the other end of the resectoscope.

Whereas formerly there was much difference of opinion regarding the type of patient who should have a resection, there is one definite common ground on which all urologists agree: Practically all believe that the small bars, contractures, small middle lobes and small intra-urethral lobes are best handled by resection, and most urologists agree

33. Kretschmer, H. L.: *The Present Trend of Transurethral Resection*, J. A. M. A. **115**:89-93 (July 13) 1940.

that the carcinomatous prostate when it produces obstruction should be handled by resection. It goes without saying that resection in a case of cancer of the prostate is much to be preferred to a permanent suprapubic fistula, even if a second and a third resection become necessary. Moreover, many patients afflicted with carcinoma of the prostate are seen so late in the course of the disease that only a small percentage are amenable to radical surgical treatment.

The only debatable point centers around the treatment of the enlarged prostate. Here opinions still differ. Surgically minded physicians have taken a definite stand that a large prostate should be removed by open operation, whereas many urologists believe that even a very large prostate should be resected. Another interesting fact is that as the experience of the operator increases the number of his resections increases and the number of his prostatectomies decreases, which is akin to stating that as the operator's experience increases the number of prostatectomies decreases because increasing proficiency permits him to resect the large prostates.

The question of whether the very large prostate should be treated by resection or by prostatectomy may automatically solve itself in the future, for the patient with prostatism will seek relief early rather than late in the course of the disease, long before the prostate reaches an enormous size and prior to the onset of the severe symptoms which occur late in the course of the disease.

Once he is aware of the fact that he may obtain relief by a method that has in its favor a low mortality rate, a much shorter period of morbidity, fewer and less serious complications and a good functional result, it is reasonable to assume that the patient of the future will seek relief early rather than late in the course of prostatic disease.

In discussing the treatment of diverticulum of the bladder and resection, Kretschmer stated that it is necessary to assume that the obstruction at the vesical neck has been removed completely. He does not remove a small diverticulum if the urine is clear and subjective symptoms are present. With a larger diverticulum, if the obstruction has been completely removed, if the patient is free of symptoms, if the urine is clear or slightly hazy owing to bacteria and contains a few pus cells and if the diverticulum is not close to the ureter so as to produce ureteral obstruction, Kretschmer concluded that administering a urinary antiseptic and keeping the patient under close observation are all that is necessary. However, if the ureter is obstructed, the pyuria does not clear up and there are recurring attacks of chills and fever accompanied with urinary symptoms, or if the diverticulum does not empty, he does a diverticulectomy. With a very large diverticulum, as a rule, he removes the diverticulum first and then performs the resection.

Hemorrhage, which in the early days occurred frequently during resection, has ceased to be much of a problem. A hemorrhage which occurs during the second postoperative week is probably always due to a secondary infection. The treatment has become standardized and consists of evacuation of clots, if present, and visualization and fulguration of the bleeding point or points. At times it may be advisable to resect the bleeding area. If the bleeding cannot be controlled, a Foley bag may be used. In cases of resected carcinoma of the prostate late bleeding is always due to a recurrence of the growth.

During the early period of resection, vasectomy was recommended and used by a large number of urologists as a routine procedure, the object of which was to prevent postresection epididymitis. At present there is a decided trend away from vasectomy as a routine procedure. In Kretschmer's first series of cases vasectomy was not employed; in 12 per cent of this series there was postresection epididymitis. He then employed vasectomy as a routine for several years. He stated that for the past three or four years he has not performed vasectomy except under certain circumstances. In his recent experience postresection epididymitis had been uncommon. He reviewed 250 recent cases taken at random from his records and found that epididymitis had developed in only 5 of them, an incidence of 2 per cent. Vasectomy is employed for patients who come to the hospital with a severe acute attack of epididymitis and are in need of catheter drainage because of complete retention or a large amount of residual urine and infected urine.

Infarction.—Hubly and Thompson³⁴ stated that infarction of the prostate gland occurs more frequently than has been commonly appreciated. They reported 3 cases illustrative of the gross and microscopic pathologic changes and of the stages through which an infarct passes, namely, from the acute to the healed, or scar, stage. The causative agents were believed to be trauma, adenomatous hyperplasia producing a distortion of the intraglandular vascular supply, prostatitis, arteriosclerosis, thrombophlebitis, circulatory stasis and embolism. They concluded that the symptoms caused by infarction in the prostate gland are mainly mechanical and that they are dependent on relative changes in the volume of the gland, which are in turn dependent on the stage of infarction present. In the early stage, when there is swelling in the involved region, symptoms of urinary obstruction may develop if the infarct is large enough. Later, when the infarct has undergone cicatrization and the prostatic volume has been thereby reduced, the symptoms of urinary obstruction may be relieved. Whether or not relief is obtained

34. Hubly, J. W., and Thompson, G. J.: Infarction of the Prostate and Volumetric Changes Produced by the Lesion: Report of Three Cases, *J. Urol.* 43:459-467 (March) 1940.

depends on the size of the infarct as compared with the size of the gland. If the infarct is large, partial prostatectomy may take place automatically.

Carcinoma.—Gutierrez³⁵ discussed the change in conception of cancer of the prostate and its treatment. Until recently urologists adopted a defeatist attitude and assumed that patients no longer amenable to prostatectomy (which meant the great majority) must face suprapubic cystostomy and with it all the sufferings entailed by a catheter-burdened life. But with the perfecting of the technic of transurethral resection there has been a growing recognition that patients with cancer of the prostate too advanced for radical operation may obtain relief of symptoms by this palliative operation, which not only is simplicity itself in the hands of one experienced in its execution but can be repeated from time to time as the symptoms may require.

With reference to the stage of development of the disease and the mode of treatment, cancers of the prostate may be divided into three groups; group 1 embraces the "silent" cancer, with no symptoms; the patients are amenable to prostatectomy. Group 2 comprises cancers which still are circumscribed within the capsule of the prostate and are still freely movable, though urinary symptoms may have appeared. The patients may also be treated by prostatectomy. Unfortunately, however, these two groups cover only about 10 per cent of cancers, and the remaining 90 per cent fall into group 3, which is made up of carcinomas so far advanced that metastasis has already occurred into the lymphatic and osseous systems when the patients are first seen by the urologist. By this time the patients usually are suffering not only from urinary symptoms but from arthritis, lumbago or some other type of pain due to invasion of nerve sheaths or of bones; in short, with generalized carcinosis. Prostatectomy is then useless, but transurethral resection may well be used for relief of urinary distress.

In view of the great number of cases in which carcinoma of the prostate has already arrived at this inoperable stage before the patient comes for treatment, all men who have reached the age of 50 years should be urged to have routine examinations of the prostate once a year, so that if the least sign of a cancerous nodule is discovered the growth may be totally removed before it becomes inoperable. Since in the early stages of the disease there are no urinary symptoms to bring them to the urologist, it is important that every general practitioner learn the technic of examination of the prostate and emphasize its importance to all elderly men who come for general physical examination. If a nodule is found, a needle biopsy will at once reveal whether or not it is carcinomatous. If the results of biopsy are positive and the roentgen

35. Gutierrez, R.: The Changing Conception of Cancer of the Prostate, *Am. J. Surg.* 48:330-341 (May) 1940.

rays show no metastasis, perineal prostatectomy at this early stage in most cases will accomplish complete cure. Such routine examinations would bring into groups 1 and 2 (operable cancer of the prostate) many growths which at present go into group 3 before the condition is recognized.

To the unfortunate patients with cancers in group 3 modern urologic practice brings the almost unfailing assurance that they may still have their urinary symptoms relieved or even wholly abated and their lives prolonged in comfort by undergoing transurethral prostatic resection. The objection traditionally raised against incision of a malignant growth has no weight in this connection, since there is admittedly no hope of cure. Metastatic extension is already present, and its avoidance is no longer a consideration. The patients can thus be saved from a catheter-burdened life, and resection may be repeated from time to time as the need arises. The use of roentgen rays is recommended for relief of pain and also for control of metastasis. About 5 per cent of the patients will not be amenable to transurethral resection, owing to impossibility of passing any kind of instrument into the urethral canal, on which the carcinoma has encroached. For these patients suprapubic drainage or, as an alternative, possible transplantation of the ureters must still remain the only means of relief.

Carcinoma of the prostate is now known to be present in about 20 per cent of all cases of prostatic obstruction and is three times as common as cancer in any other internal organ of the male. Under this new conception of its management the prognosis for a five year cure is greatly improved.

Kickham³⁶ emphasized several striking features of carcinoma of the prostate. These are: (1) its extremely high incidence, (2) the insidiousness of its onset, (3) the viciousness of its local extension and metastatic dissemination, (4) the deceptiveness of its clinical manifestations, (5) the extreme difficulty of early diagnosis and (6) the utter hopelessness of cure unless the lesion is recognized in the early stages and unless prompt measures directed to complete eradication are adopted in these early stages.

Postmortem examination was carried out in 132 of Kickham's series of carcinomas of the prostate. Analysis revealed that 63 autopsies (54.2 per cent) showed obstructive changes in the upper portion of the urinary tract secondary to direct or indirect ureteral occlusion by malignant growth. The obstruction was bilateral in 47 instances and unilateral in 16. In 58 cases (44 per cent) there was sufficient renal damage from the effects of urinary obstruction and urosepsis to constitute an adequate

36. Kickham, C. J. E.: *Diagnostic Pitfalls in Carcinoma of the Prostate*, J. Urol. **45**:92-101 (Jan.) 1941.

cause of death. The results of postmortem examination have demonstrated definitely that impairment of renal function is the most common cause of death from carcinoma of the prostate. Metastatic disease in the postmortem studies was found in the regional lymphatics in 73 cases (63 per cent). Other organs involved were the liver, in 27 cases (23 per cent); the lung, in 17 cases (15 per cent), and the kidney, in 7 cases (6 per cent). Involvement of the bladder was recorded in 30 cases (26 per cent) and invasion of the rectum in 12 cases (9 per cent).

Digital examination of the rectum is the "sine qua non" in the establishment of the diagnosis of prostatic cancer. The greatest significance must be attached to hardness of the gland, whether diffuse or localized, as this is suggestive of carcinoma.

Metastasis to bones was demonstrated in 58.7 per cent of cases. In 87 per cent of these metastasis was shown by roentgen rays in the bones of the pelvis. The lumbar portion of the spine was the site of the deposits in 55 per cent.

SURGERY OF THE KIDNEY

Preoperative and Postoperative Care.—Priestley and Schulte³⁷ considered the subject of preoperative and postoperative care for patients who undergo operations on the kidney. They pointed out that, although this care is similar in many respects to the care of any general surgical patient, there are certain special considerations that should be kept in mind.

The total and the relative function of the two kidneys should be determined as accurately as possible preoperatively. For this purpose the use of excretory urographic study is a great help provided that renal function is within normal limits or only slightly reduced. In the event that there is obstruction, such as that due to a stone impacted at the ureteropelvic juncture, a delayed plain roentgenogram of the urinary tract taken a few hours or even a day after the injection of the medium intravenously may afford the necessary information. In some cases cystoscopic study and catheterization of each kidney may be necessary to determine the information required. In any event, in each case the blood urea should be determined, and in some cases the values for carbon dioxide-combining power, creatinine and blood chlorides should also be determined. An elevation of the concentrations of blood urea and creatinine and a lowered carbon dioxide-combining power will be found in patients with poor renal function. There is almost always associated secondary anemia, and the patient usually is weak and has a poor appetite. Preoperative treatment should include a generous

37. Priestley, J. T., and Schulte, T. L.: *Preoperative and Postoperative Care for Patients Who Have Operations on the Kidney*, S. Clin. North America 20: 1049-1059 (Aug.) 1940.

supply of fluid administered intravenously (physiologic solution of sodium chloride and 5 per cent or 10 per cent dextrose alternately). When definite acidosis is present the value of the carbon dioxide-combining power is materially lowered, and it is well to administer 5 per cent solution of sodium bicarbonate intravenously. The amount of sodium bicarbonate necessary may be computed by a mathematical formula; however, it is best never to give more than 500 cc. of 5 per cent solution at any one time.

If severe anemia is present, multiple blood transfusions are of distinct benefit. If serious infection is present, treatment with an appropriate urinary antiseptic may be employed judiciously. But in some cases treatment of this type produces anorexia and nausea, and the ultimate effect on the patient's general condition is detrimental. If there is marked obstruction to one or both kidneys, particularly in the presence of a certain degree of renal insufficiency, drainage with an indwelling ureteral catheter may be beneficial.

In cases of nephrolithiasis it is important to know the size, contour and number of calculi present, as well as their exact location within the kidney. Also, the patient should be investigated to detect any evidence of dietary or vitamin insufficiency, endocrine disturbance or metabolic disorder. The presence or absence of infection should be ascertained by appropriate methods. The concentration of urinary calcium as well as the presence of cystine in the urine should be determined if indicated. The management of the patient with hydronephrosis requires accurate information concerning the relative function of the two kidneys; furthermore, infection, if present, should be reduced to a minimum before operation is considered. Catheterization for uninfected hydronephrosis may be undesirable unless immediate operation is planned.

The anesthesia of choice usually is spinal, induced with procaine hydrochloride; however, if the patient is a good surgical risk, an inhalation anesthetic may be suitable. On the other hand, if he is a poor risk, the use of pentothal sodium with local infiltration at the site of the incision with procaine hydrochloride is employed.

Concerning postoperative considerations, it is well to withhold all orally taken fluids for at least thirty-six to forty-eight hours after operation, and then they may be given in small amounts, such as $\frac{1}{2}$ ounce (15 cc.) of water per hour until the patient demonstrates his ability to tolerate fluid. Such a plan will obviate abdominal distention, which is easier to prevent than to treat. The fluid intake should be about 3,000 to 4,000 cc. daily. If renal function is poor, larger amounts may be necessary. If nephrectomy has been performed it is well to determine the value for blood urea at some time during the early postoperative period.

Drains, usually of the Penrose type, are left in place for at least seven days; if the operative field has been grossly contaminated they are left in place longer. In cases of tuberculosis in which nephrectomy has been performed no drains are used.

The postoperative treatment of patients with renal insufficiency requires care in the prevention of pulmonary edema from intake of too much fluid. This is best done by determining the concentration of blood urea, the carbon dioxide-combining power and the urinary output and balancing these observations against the amount and type of fluid to be used intravenously. Particular attention must be paid to the gastrointestinal tract, as anorexia and nausea are common. Under these circumstances, foods which appeal to the patient are often better tolerated and more valuable than any special diet selected by the physician.

Nephrostomy tubes are connected by a closed aseptic system to a sterile bottle at the side of the bed. Postoperatively the tube should be irrigated with warm boric acid solution often enough to prevent blood clots from forming and plugging the tube. If there is an appreciable amount of infection, lavage with some particular type of solution, such as phosphoric acid (0.25 per cent to 0.5 per cent), acetic acid (1 to 3,000) or potassium permanganate (1 to 8,000), may be employed.

In order to prevent the recurrence of renal calculi it is important that all stones be removed at the time of operation, that any factor which predisposes to obstruction at the ureteropelvic juncture be corrected and that a nephrostomy tube be inserted if it appears desirable. Subsequently, chemical analysis of the stones should be carried out; the amount of calcium in the urine should be determined, and any infection in the urinary tract should be eradicated. Furthermore, distant foci of infection should be cleared up. The patient should be studied for vitamin deficiency, endocrine abnormality and metabolic disorder. Prior to dismissal of the patient a plain roentgenogram should be made in order to make certain that no stones are present. Periodic examinations should be conducted subsequently.

The question of irradiation also was considered by Priestley and Schulte. They expressed the opinion that irradiation is of questionable value preoperatively or postoperatively for patients who have hypernephroma and is of no value in cases of squamous cell epithelioma of the renal pelvis. It appears to be of value both preoperatively and postoperatively in the treatment of children with a Wilms tumor.

Finally, they considered management after plastic operations in cases of hydronephrosis. They expressed the opinion that the ureteral splinting catheter and the nephrostomy tube should be left in place for two to three months after the operation and that it is safer to err by leaving the tubes in too long than by removing them too soon.

TESTIS

Tumor.—Gilbert and Hamilton³⁸ reviewed more than 7,000 case records of testicular malignant disease in an attempt to define the relation of testicular ectopy to testicular cancer. In 840 of the 7,000 cases of cancer (approximately 11 per cent) the cancer was associated with ectopy. That 11 per cent of all testicular tumors occur in the 0.23 per cent of males who are cryptorchid proves that neoplastic growth occurs more commonly in ectopic than in scrotal testes, about forty-eight times more often than would be expected from chance association.

In 96.8 per cent of cases of unilateral cryptorchidism and one testicular tumor the tumor was in the undescended testis. In 69 cases of bilateral cryptorchidism and cancer of the testes the tumors were bilateral in 24.6 per cent as against a bilaterality of only 0.7 per cent in approximately 6,200 cases in which the tumors occurred in scrotal testes. Thus the condition of the opposite testicle when one is affected by malignant disease in the presence of bilateral cryptorchidism is a matter of grave concern and presents a dilemma similar to that encountered with unilateral ovarian and mammary cancer.

Despite this apparent correlation between testicular ectopy and testicular malignant disease, it is not proved that the ectopy is carcinogenic or that cancer is the result of an abnormal condition in any particular site in which the testicle may be lodged. Also, there is no evidence that any particular site of ectopy or even the condition of ectopy hastens carcinogenesis. The average age at which testicular malignant disease is observed and the relative incidence at various ages are almost identical for abdominal and inguinal testicular ectopy. The average age of appearance is 31 years for scrotal as compared to 34 years for ectopic testes.

Gilbert and Hamilton concluded that the predisposition to cancer of the testicle can be better correlated with congenital conditions as a whole than with an ectopic site alone, which is only one of the congenital anomalies. Congenital hernia and pseudohermaphrodisism are common. Of 345 patients who had abdominal testicular tumors, 11 per cent were pseudohermaphrodites. In patients with cancer of the testes congenital defects associated with other than the reproductive organs included such conditions as cleft palate and harelip, but these were not as common as hernia, pseudohermaphrodisism and ectopy.

A question often raised as to the management of cryptorchidism is whether or not orchiopexy lowers the incidence of testicular malignant disease. There had been reported 77 cases of malignant disease in which

38. Gilbert, J. B., and Hamilton, J. B.: *Studies in Malignant Testis Tumors: III. Incidence and Nature of Tumors in Ectopic Testes*, Surg., Gynec. & Obst. **71**:731-743 (Dec.) 1940.

orchiopexy was performed. This number may be said to be relatively few, and the results of orchiopexy have been in the main free from malignant complication. But until more specific data are available there can be no foundation for the assumption that orchiopexy may lower the incidence of malignancy. The rationale for orchiopexy must rest on the placement of testicles where they can be more closely observed, the repair of hernias that commonly accompany cryptorchidism and the encouragement of spermatogenesis and possibly also of increased hormone secretion.

Abdominal placement of testes which were seemingly impossible to put into the scrotum was followed in 14 cases by reports of tumors. Such occurrences in testes resident in the abdomen make surgical judgment in the individual case a choice between the danger of carcinogenesis and the benefits to be obtained from secretion of the testicular hormone; spermatogenesis in abdominal testes can scarcely be expected.

In view of the significance of the correlation between testicular cancer and ectopy, Gilbert and Hamilton³⁸ made a complete collection of reports on cancer of the testis. Their analysis of 841 cases brings out the following points:

Patients who have cancer of the testis commonly exhibit congenital defects, such as ectopy, hernia and pseudohermaphrodisism.

Cancer of the testis is associated with ectopy as follows:

1. In 11 per cent of recorded cases of cancer of the testis there is concomitant ectopy, a correlation forty-eight times higher than would be expected by chance association.

2. Among the patients who have cancer of one testis and unilateral cryptorchidism, 97.5 per cent of the tumors are in the ectopic testis.

3. Of bilaterally cryptorchid men who had cancer of one testis, 24.6 per cent later had a tumor in the second testis, whereas men with both testes in the scrotum subsequently had a tumor in the second testis in but 1 per cent of the cases. The frequency of bilateral involvement of ectopic testes is thirty-two times that of involvement of scrotal testes.

Ectopy is not necessarily the cause of cancer. 1. Cancer appears at an earlier average age in cases of scrotal than in cases of ectopic testes, 31 as compared with 34 years; it does not appear that ectopy hastens carcinogenesis. 2. A tumor occurred in the descended but not in the undescended testis in 23 cases of unilateral cryptorchidism. 3. No particular tumor type is favored by an ectopic site. 4. The predisposition to cancer of the testis can be better correlated with congenital conditions than with an ectopic site.

The incidence of cancer of the testis is highest during the reproductive years, being markedly greater from puberty until about the sixtieth year and reaching a peak in the thirty-fifth to the thirty-ninth year. This

is true not only with regard to the percentage incidence of cancer of the testis in the various age groups but with regard to the number of living males in these age groups. Between the twenty-fifth and the fifty-ninth year the percentage incidence is almost double, and from the thirty-fifth to the thirty-ninth year almost triple that expected by chance visitation in living males.

The undescended testis must be regarded from the viewpoint of potential malignant disease and as an organ unfavorably situated for spermatogenesis but conducive to herniation. Orchidopexy is not the complete answer, for 77 tumors have been observed in testes previously transferred to the scrotum from an ectopic position. The incidence of cancer in the second testis (subsequent to involvement of one testis) is approximately 1 in 100 cases of scrotal testes and almost 1 in 4 in cases of bilateral cryptorchidism. These facts direct attention on the second testis when one testis is known to be malignant and are equivalent to ordering continued observation in patients with ectopy. Even in men who are not cryptorchid the possibility of involvement of the second testis after the occurrence of cancer in one testis is a matter of import, for the frequency of bilateral tumors is some 770 times the incidence of cancer in either testis among the general male population.

Barringer and Earl³⁹ discussed teratoma testis, giving a survey of 37 postmortem records.

The 37 patients who died of teratoma testis ranged in age between birth (1 was a stillborn infant) and 47 years.

Metastasis may be and generally is both lymph borne and blood borne.

If a left supraclavicular signal node is present, there is probably a metastatic chain of nodes along the course of the thoracic duct.

The lungs were involved in 78 per cent of cases. When there was pulmonary involvement the liver was affected in 75 per cent of the cases. The genitourinary tract was involved in 24 per cent of all cases. When there was pulmonary metastasis the mediastinal nodes were involved in 55 per cent of cases.

In nearly all of these cases there was bilateral involvement of the abdomen, either of the lymphatic glands or of intra-abdominal organs, namely, the liver, the kidneys or the spleen.

Counseller, Nichols and Smith⁴⁰ reported that up to the time of their report 47 cases of anorchia could be found in the literature; in 11 the condition was bilateral, and in 36, unilateral. Since 1931, when 2 cases

39. Barringer, B. S., and Earl, D.: Teratoma Testis: Survey of Thirty-Seven Autopsy Records, *Surg., Gynec. & Obst.* **72**:591-600 (March) 1941.

40. Counseller, V. S.; Nichols, D. R., and Smith, H. L.: Congenital Absence of Testis: A Report of Seven Cases of Monorchidism, *J. Urol.* **44**:237-241 (Aug.) 1940.

of bilateral anorchidism were observed at the Mayo Clinic and were reported by Counseller and Walker, 7 additional cases had been observed at the clinic. In these 7 cases each of the patients was 21 years of age or less. In all but 1 case a vas deferens was found. It was frequently necessary to open the peritoneum in order to exclude definitely the presence of a testis. In 4 of the 7 cases absence of the testis occurred on the left side and in 3 on the right.

Biopsy.—Charny⁴¹ stated that testicular biopsy is a simple, innocuous procedure, basing his opinion on its application in the cases of 40 infertile patients without a single mishap. Testicular biopsy is not only a definite diagnostic aid in differentiating between obstructive and nonobstructive seminal defects but serves a prognostic function. When performed before and after treatment, testicular biopsy yields the most direct evidence of the efficiency of the therapeutic agent employed.

URETHRA

Infection.—Knight, Uhle and LaTowsky⁴² reported a study of the results of sulfathiazole treatment of gonorrheal urethritis in the male. A total of 55 patients were studied, 50 of whom were followed to the completion of the study. Of the 50 patients followed, 96 per cent were cured by an average of eight days' treatment with an average dose of 28 Gm. of the drug. Toxic reactions occurred in only 11.5 per cent of the cases. The average time required for bacteriologic cure was twenty-eight days. The criteria of cure in this study were strict and included as the final provocative test two or more sterile smears and cultures of the prostatic fluid. Sulfathiazole was found to be a particularly valuable drug for the treatment of gonorrheal urethritis in the male, not only because of its therapeutic efficiency but because of the low incidence of toxic reactions encountered.

Gonococcic Infection.—Van Slyke, Wolcott and Mahoney⁴³ stated that there are obvious objections to the general use of sulfanilamide as an agent in the treatment of gonococcic infection.

Sulfapyridine was used in 300 cases of gonococcic infection. The rate of cure approximated 85 per cent for patients who had not received previous chemotherapy and 70 per cent for those who had failed to

41. Charny, C. W.: *Testicular Biopsy: Its Value in Male Sterility*, J. A. M. A. **115**:1429-1432 (Oct. 26) 1940.

42. Knight, F.; Uhle, C. A. W., and LaTowsky, L. W.: *The Treatment of Gonorrheal Urethritis in the Male with Sulfathiazole*, J. Urol. **44**:748-752 (Dec.) 1940.

43. Van Slyke, C. J.; Wolcott, R. R., and Mahoney, J. F.: *The Chemotherapy of Gonococcic Infections: I. Summary of Experience with Sulfanilamide; II. Investigation of Chemotherapeutic Effect of Sulfapyridine*, J. A. M. A. **116**:276-280 (Jan. 25) 1941.

benefit by earlier sulfanilamide treatment. Subclinical carrier states were not encountered among patients treated with sulfapyridine.

The larger doses (6 Gm. a day) were not more efficacious than the smaller ones (2 Gm. a day). Toxic responses were milder and less frequent in the patients who received the smaller doses.

Toxic manifestations were not serious and were significantly less than those resulting from administration of sulfanilamide.

Prolonged administration is not indicated. Sulfapyridine therapy should be limited to ten days or less.

Sound clinical judgment alone can serve as a practical guide to the use of sulfapyridine in the treatment of gonococcic infection if the lack of laboratory facilities would otherwise curtail the use of the drug. Treatment with sulfapyridine appears applicable to the comprehensive therapeutic needs of the disease.

Rupture.—Harrison⁴⁴ discussed the methods used in the treatment of 21 patients who had injuries of the urethra. Twelve of these had injury of the bulbous portion of the urethra. Nine patients had rupture of the membranous portion of the urethra as a result of fractures of the pelvic bones.

The best results for rupture of the bulbous portion have been obtained by immediate external urethrotomy, whereas the operative management of rupture of the membranous portion consists of a combined suprapubic and perineal approach, particularly when the rupture is accompanied with fracture of the pubis and ischium.

TORSION OF THE APPENDIX TESTIS

Scott⁴⁵ reported a case of torsion of the appendix testis and stated that this condition may account for many of the cases of so-called epididymo-orchitis occurring during childhood and adolescence. The treatment should always be surgical, as operation is without risk and recovery from conservative treatment requires more time than does recovery from surgical treatment.

URACHAL CALCULUS

Wyatt and Lanman⁴⁶ reported the finding of a calculus in the urachus of a white boy aged 7 years. The main difficulty experienced by the

44. Harrison, J. H.: The Treatment of Rupture of the Urethra, Especially When Accompanying Fractures of the Pelvic Bones, *Surg., Gynec. & Obst.* **72**: 622-631 (March) 1941.

45. Scott, R. T.: Torsion of the Appendix Testis, *J. Urol.* **44**:755-758 (Dec.) 1940.

46. Wyatt, G. M., and Lanman, T. H.: Calculus in Urachus: Report of Case with Enuresis, *Am. J. Roentgenol.* **43**:673-675 (May) 1940.

patient was incontinence. A roentgenogram showed a calculus in the upper region of the bladder. The stone was found embedded in the center of the mass, which was removed through a midline suprapubic incision. The diagnosis was calcification and ossification of a remnant of a urachal cyst. The patient recovered readily, and shortly after the operation his urinary control became normal.

SQUAMOUS CELL CHANGES IN THE URINARY TRACT

Scholl⁴⁷ stated that squamous cell changes of the mucous membrane lining the urinary tract are generally associated with infection and localized trauma. Two cases were reported in which there was evidence of long-standing urethral obstruction and infection of the urinary tract. In 1 case symptoms had been present for eleven years; in the other, for twenty-five years. In 1 of the cases reported there was an extensive squamous cell carcinoma which had deeply infiltrated most of the vesical wall. In the other case widespread leukoplakial areas were found in the mucous membrane of the bladder, the ureter and both renal pelves. Malignant changes were found in the vesical plaques.

Neither of the patients had received treatment for his urinary infection during the many years of what was possibly a premalignant period. It is probable that early institution of the usual methods of treatment would have diminished the extent of the urinary obstruction and infection and possibly would have arrested the process of metaplasia before it had advanced to an irreversible stage. Although leukoplakia and squamous cell carcinoma occur only rarely as complications of obstruction and infection, their possible occurrence is one more reason for continued effort by the members of the medical profession to reduce or eradicate these commonly seen and persistent infections of the urinary tract.

UROGRAPHY

Arendt and Maslow⁴⁸ stated that by filling the bladder with from 150 to 250 cc. of oil they were able to prevent intravenously injected dye from reaching the bladder, thus keeping it back in the ureters and pelves without need of any outside compression. They thus had (1) a more complete filling of the pelves and the calices; (2) less spastic and reflex contractions of the pelves and the ureters, and (3) a clear outline of the lower pelvic portions of the ureters, which are usually obscured by the

47. Scholl, A. J.: Squamous Cell Changes and Infection in the Urinary Tract, *J. Urol.* **44**:759-767 (Dec.) 1940.

48. Arendt, J., and Maslow, L. A.: Blocking of the Ureters in Intravenous Pyelography by Means of Filling the Bladder with Oil, *Radiology* **35**:350-352 (Sept.) 1940.

dye in the bladder. The procedure is simple and harmless when contraindications are observed.

Shiflett and Keith⁴⁹ stated that the lateral pyelogram has a wide range of usefulness. The technic is simple and does not appreciably delay the urologist or add to the discomfort of the patient. The normal variable is much less than in the average system, which makes it relatively easy to detect pathologic changes. It permits convincing topographic differentiation of intra-abdominal and retroperitoneal tumors and also differentiation of retroperitoneal lesions themselves and can be used to advantage in roentgen investigation of all problems relating to the urinary tract. Elective lateral pyelographic study is of as much value as the lateralization of any organ or system of organs other than the kidneys and should be placed on an equal plane.

Nichols⁵⁰ stated that he has been interested in lateral pyelography, particularly in the diagnosis and location of suspicious shadows in the region of the kidneys. Often dense shadows which appear to be calculi lost in the pyelographic medium on an anteroposterior exposure are found, when a pyelogram is made, to be shadows either posterior or anterior to the kidney. Therefore, Nichols employs lateral pyelograms almost routinely when renal calculi are suspected if they are not definitely identified by either a pyelogram or an excretory urogram. Nichols stated that he also finds this procedure a valuable adjunct to examination for suspected perinephritic abscess.

STERILITY

Kreutzmann⁵¹ stated that all cases of sterility in the male can be divided into two groups, urologic and endocrinologic. In the urologic cases the condition is either congenital or acquired.

At present it is only in cases of hypothyroidism that consistently good results are obtained. The administration of large doses of testosterone propionate causes marked decrease in the number of spermatozoa per cubic centimeter. The injection of 5 mg. of testosterone propionate three times a week for one month caused no appreciable change in the percentage of abnormal forms in patients with either normal or abnormal sperm counts. Repeated sperm analyses should be made during treatment to guard against transient or possible permanent damage to the spermatogenic structures of the individual patient.

49. Shiflett, E. L., and Keith, D. Y.: *Lateral Pyelography*, *Am. J. Roentgenol.* **43**:664-671 (May) 1940.

50. Nichols, B. H., in discussion on Shiflett and Keith.⁴⁹

51. Kreutzmann, H. A. R.: *Sterility in the Male: Diagnosis and Treatment*, *J. A. M. A.* **115**:1424-1426 (Oct. 26) 1940.

News and Comment

Statement Concerning the New "Progress in Orthopedic Surgery."—"Progress in Orthopedic Surgery" is now sponsored by the American Academy of Orthopaedic Surgeons and is being prepared under the direction of its editorial committee. It is to be published only once a year and will include a survey of the literature for the preceding year. An editorial board of twenty-two orthopedic surgeons, representing twenty-one clinics from all sections of the country, has been appointed. The chairman of this editorial board has selected from the *Quarterly Cumulative Index Medicus* of 1940 the titles of 1,793 articles of orthopedic interest. Each editor has been assigned a subject, to which in most instances either he or the clinic he represents has made definite contributions in the past. The assistance of many younger men in these clinics and of others has been used in the preparation of the material. Only those articles which appear to the editor preparing the section to represent definite progress or to be of unusual interest and to warrant attention have been used in the final proof. This new "Progress" will be from two to three times as large as the total size of the former reports and will contain about 80,000 words, representing about 750 articles.

The following are the 20 sections of the "Progress," each prepared by a separate editor:

1. Congenital Dislocation of the Hip
2. Other Congenital Deformities
3. Diseases of Growing and Adult Bone
4. Tuberculosis of Bones and Joints
5. Infections of Bones and Joints, Exclusive of Tuberculosis
6. Chronic Arthritis
7. Infantile Paralysis
8. Neuromuscular Disorders, Exclusive of Infantile Paralysis
9. Fresh Fractures and Dislocations
10. Fracture Deformities
11. Bone Tumors
12. Diseases Low in the Back
13. Diseases of the Spine, Exclusive of Those Low in the Back
14. Diseases of the Hip
15. Diseases of the Knee
16. Diseases of the Foot and Ankle
17. Diseases of the Shoulder, Neck and Jaw
18. Diseases of the Elbow, Forearm, Wrist and Hand
19. Apparatus, Technic and Amputations
20. Research

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PROBLEM OF ANOXIA IN SURGERY AND ANESTHESIA

REPORT OF EXPERIMENTAL AND CLINICAL CASES AND
REVIEW OF THE LITERATURE

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AND

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"Anoxemia not only stops the machine but wrecks the machinery." Only a great pioneer in the study of respiration like Haldane¹ could have spoken such truth. His words should be foremost in the mind of every surgeon dealing with a patient in shock. They should be foremost in the mind of every anesthetist dealing with a narcotized patient, because asphyxia is one of the dangers present in all forms of anesthesia. The health and the very life of the patient depend on the surgeon's knowledge and skill in preventing and averting anoxia. The number of deaths under anesthesia is appalling. Jarman² collected statistics from the hospitals of all the English-speaking countries. He received detailed reports of nearly 1,300 deaths under anesthesia between 1921 and 1939. Of this series of approximately 1,300 detailed cases the following classifications were made: When the anesthetic was specified the number of deaths under ether anesthesia alone was 130; under spinal anesthesia, 81; under nitrogen monoxide, oxygen and ether anesthesia, 50; under chloroform anesthesia alone, 29; under intravenous anesthesia, 21. Procedures during which the death occurred included operations for acute conditions within the abdomen (121); operations on the brain (70); appendectomies (65); gynecologic operations (61); operations on the thyroid (43); obstetric procedures (43), and operations for nonacute abdominal conditions (35). The remainder of the deaths

From the Department of Surgery and the Hixon Laboratory of Medical Research, University of Kansas Hospitals.

1. Haldane, J. S.: Anoxemia, *Brit. M. J.* 2:65, 1919.

2. Jarman, R.: Deaths Under Anesthesia from 1921 to Present Date, *Brit. J. Anesth.* 16:100, 1939.

occurred during operations on the tonsils, the mastoids and the chest and during orthopedic procedures. About 264 deaths have been associated with 8,000,000 administrations of intravenous anesthesia. There are undoubtedly many more unreported anesthetic deaths. The cases of nonfatal asphyxia with subsequent personality, mental and neurologic changes are also probably numerous.

It can be said that all deaths in their final analysis are due to anoxia. Present day knowledge of anesthesia and shock, gained from fundamental experiments in the laboratory and clinical observations, is doing much to prevent accidental premature anoxia and death or cerebral degeneration. Much has been learned from the detailed studies of anesthetic fatalities reported by Courville³ and by Hartman.⁴ The specter of anoxia is present even at birth. Schreiber and Gates⁵ have called attention to the occurrence of cerebral damage in infants when a combination of narcotics and nitrogen monoxide anesthesia is used during labor. It is hoped that more disseminated knowledge of anoxia and its consequences will help to prevent the mortality and morbidity of anoxia accompanying operation and anesthesia. For this reason we present the following analysis of 2 clinical cases in which death occurred and of 2 cases of experimental cerebral degeneration due to anoxia in dogs. The literature pertaining to the anoxia produced by the different anesthetic agents is also reviewed.

REPORT OF CASES

CASE 1.—A 58 year old white man had an ailment clinically diagnosed as carcinoma of the stomach. On his admission to the hospital his red blood cell count was 1,850,000 per cubic millimeter and the hemoglobin content was 31 per cent. Multiple blood transfusions elevated the erythrocyte count to 4,100,000 and the hemoglobin level to 77 per cent. Preoperative medication consisted of 1.5 grains of pentobarbital sodium, $\frac{1}{2}$ grain (0.01 Gm.) of morphine sulfate and $\frac{1}{200}$ grain (0.3 mg.) of scopolamine hydrobromide. At the time of operation he received 100 mg. of procaine hydrochloride and 5 mg. of pontocaine hydrochloride intraspinally, in the third lumbar space. The sensory anesthesia ascended to the fourth thoracic level. This anesthetic was supplemented with a mixture of 50 per cent nitrogen monoxide and 50 per cent oxygen. An exploration of the abdomen was then done. Twenty minutes later, during which time he received about 150 cc. of physiologic solution of sodium chloride intravenously, the patient went into shock. The blood pressure could not be determined; the respirations stopped, and the patient showed gray cyanosis. Artificial respiration and inhalations of 95 per cent oxygen and 5 per cent carbon dioxide were started imme-

3. Courville, C. B.: (a) Asphyxia as a Consequence of Nitrous Oxide Anesthesia, *Medicine* **15**:129, 1936; (b) Ether Anesthesia and Cerebral Anoxia, *Anesthesiology* **2**:44, 1941.

4. Hartman, F. W.: Some Etiological Factors and Lesions in Cerebral Anoxia, *Am. J. Clin. Path.* **8**:629, 1938.

5. Schreiber, F., and Gates, N.: Cerebral Injury in the New Born Due to Anoxia at Birth, *J. Michigan M. Soc.* **37**:145, 1938.

diately. He also received 1.5 cc. of coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide), 1 cc. of adrenal cortex extract intravenously and 0.5 cc. of a 1 per cent solution of neo-synephrin hydrochloride (5 mg.) intramuscularly. The intravenous administration of fluid was accelerated so that when spontaneous respirations were resumed (after twenty-five minutes) he had received an additional 200 cc. of physiologic solution of sodium chloride. The systolic blood pressure came back to 50 mm. of mercury. The patient then had pulmonary edema, and rales were heard all over the chest. Twenty-five per cent dextrose was substituted for the physiologic solution of sodium chloride. An inoperable carcinoma of the stomach with metastases to the liver was found at operation. On the patient's return to his room, administration of oxygen by nasal catheter (8 liters per minute) was started. His blood pressure remained below 60 mm. of mercury for over an hour and a half and then slowly rose to 118 systolic and 80 diastolic in two and one-half hours. The patient did not react from the

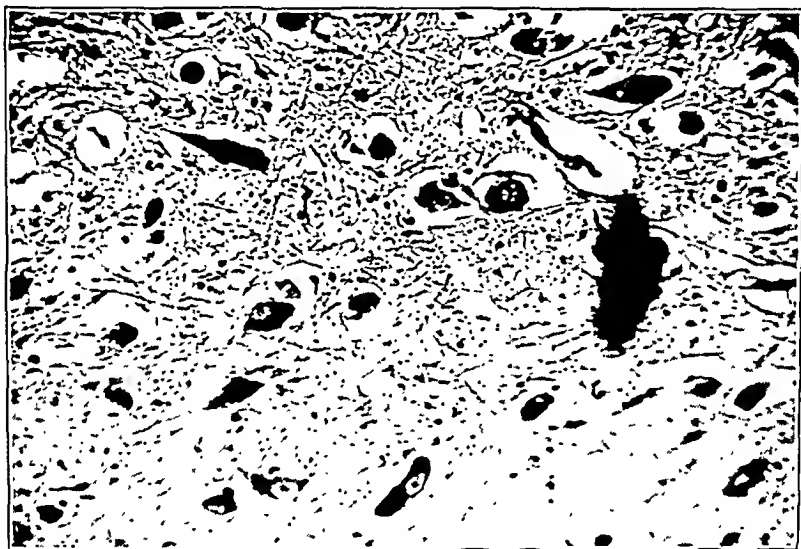


Fig. 1 (case 1).—Section of the cerebral cortex, showing a loose, vacuolated matrix and an increase in size of the pericellular spaces. The nerve cells show various stages of degeneration and pyknosis. Some nuclei have undergone chromatolysis. (Low power.)

anesthetic until the following day. He remained comatose for several days and irrational until death, which occurred on the twenty-first postoperative day. During this time he showed evidence of extensive cerebral damage. Twelve hours after the operation he was still unconscious and did not respond to vocal or tactile stimuli. The blood pressure was 130 systolic and 80 diastolic; the pulse rate was 136; the respiratory rate was 30, and the rectal temperature was 100.8 F. He had some fine fibrillary muscular twichings and later some generalized convulsions. His pupils were round, regular and equal. They reacted sluggishly to light. He had a fixed stare. Increased muscle tone was present, and all of the deep reflexes were hyperactive. Ankle clonus and Babinsky, Gordon and Oppenheim reflexes were present. The superficial reflexes were absent. Spinal puncture showed the fluid to be under normal pressure. The patient had a slurred speech. He had incontinence of his sphincters and no voluntary muscular coordination. A week

before death the deep reflexes were still exaggerated and pathologic toe reflexes were present.

Autopsy.—The brain showed typical anoxic changes. The vessels of the meninges were somewhat congested and enlarged. The dome of the brain showed moderate amounts of clear edema fluid beneath the meninges. Section through the cerebral substance revealed an area of cystic degeneration about 1 cm. in diameter, located in the left anterior hypothalamic area near the foremost part of the internal capsule. Histologic section of the cortex revealed varying degrees of anoxic degeneration. Some areas showed shrunken, pyknotic nerve cells. Mild degeneration was evidenced by agglutination of the Nissl substance, chromatolysis of the nuclei, pyknosis of the nerve cells and increased size of the pericellular spaces (figs. 1 and 2). There was also an increase in the perivascular spaces. In many instances these contained red blood cells (fig. 3). The stroma of the brain

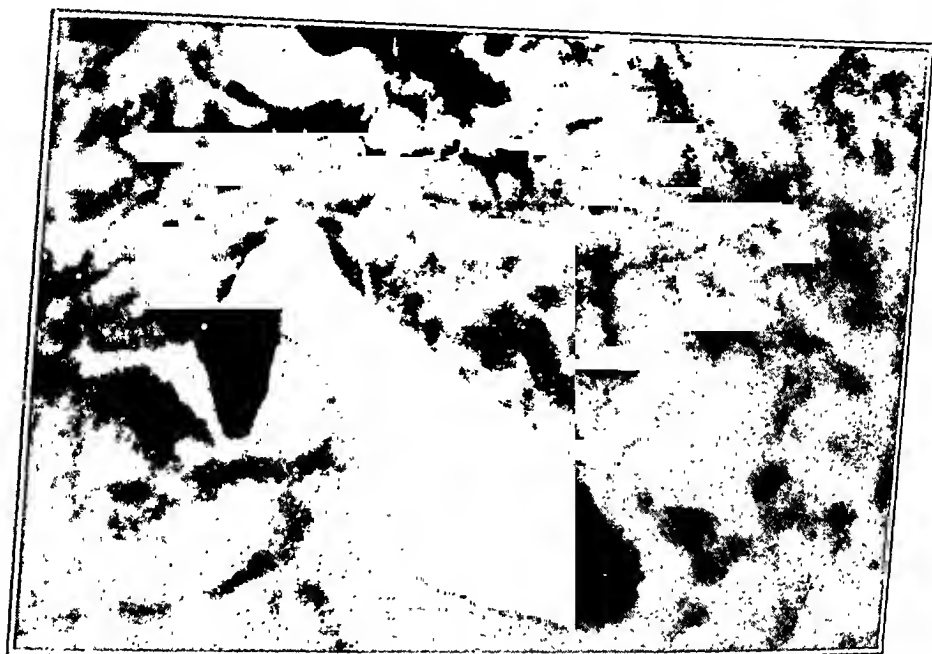


Fig. 2 (case 1).—Early degenerative changes in a section of the brain. The Nissl substance has granulated and clumped. The stroma is loose, and the pericellular space is enlarged. (High power.)

was loose and vacuolated. In some areas devastation necrosis of large numbers of nerve cells was seen.

Comment.—This patient was suffering from chronic anemic anoxemia because of a low level of hemoglobin (31 per cent) on admission to the hospital. It is interesting to note that his family reported that he had shown some mental aberrations before admission to the hospital. The patient was often disoriented and had a poor memory for recent happenings. These mental changes were probably due to the profound anemic anoxemia. Anoxia at the time of operation resulted from a number of contributory factors. The preoperative medication (with pentobarbital sodium, morphine sulfate and scopolamine hydrobromide) produced mild anoxemia and a mild degree of direct histio-

toxic action on the brain tissues. The spinal anesthesia, which rose to the fourth thoracic level, resulted in a loss of vasomotor and muscular tone, so that stagnant anoxia developed because of the fall in blood pressure. A tendency toward anoxic anoxemia developed with the impairment of respiration due to paralysis of the intercostal muscles. The nitrogen monoxide and oxygen supplementing the spinal anesthesia probably had no anoxic effect, because 50 per cent oxygen was given in the mixture. The development of pulmonary edema, however, did produce severe anoxic anoxemia, because, even though the patient was treated with 95 per cent oxygen, edema of the alveolar walls and fluid in the alveoli decreased the absorption of oxygen. The intravenous

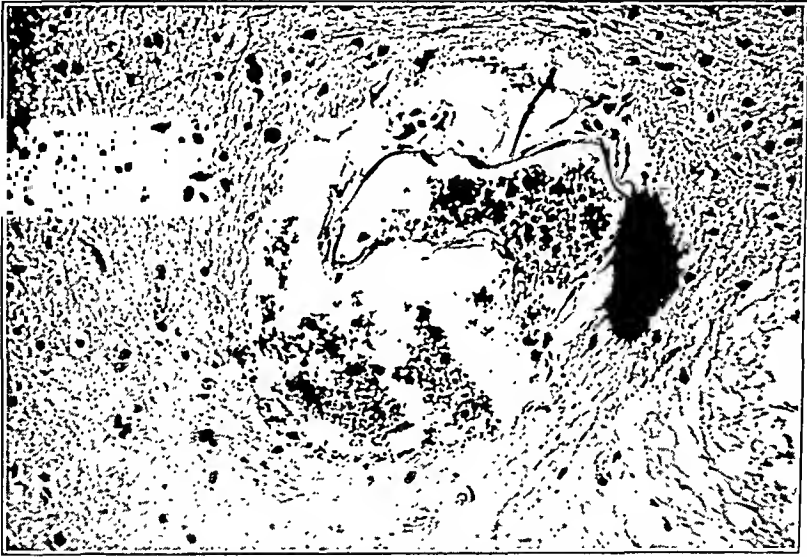


Fig. 3 (case 1).—Section of the brain, showing a marked increase in the perivascular space and the presence of blood cells outside the vessel wall. The stroma is loose. (Low power.)

administration of fluids to patients in this condition or to patients with mild impairment of renal and cardiac function is of considerable importance. With the fall in blood pressure renal activity probably ceased. In an attempt to restore the blood pressure the patient was given 0.5 cc. of neo-synephrin hydrochloride intramuscularly and about 350 cc. of physiologic solution of sodium chloride intravenously. In causing a generalized vasoconstriction the neo-synephrin probably helped to restore the blood pressure, but at the same time vasoconstriction in the kidney caused a cessation of excretion of urine, so that the intravenous fluid was retained. We have noted this effect of neo-synephrin on the kidney recently in dogs in our laboratory. Finally, the increased permeability of the capillaries due to anoxemia facilitated the development of pul-

monary edema. Landis⁶ has reported increased permeability of the capillaries in the mesentery of the frog during anoxemia. Immediately after a three minute period of oxygen lack, fluid filtered through the capillary wall at about four times the normal rate. The increased permeability of the wall also permitted the passage of protein, thus reducing the effective osmotic pressure of the plasma proteins to almost half the normal value.

Thus all of the types of anoxemia played a part in the cerebral anoxia and death of our patient: anemic anoxemia on the basis of a low preoperative level of blood hemoglobin; stagnant anoxemia due to shock and to spinal anesthesia, and anoxic anoxemia due to pulmonary

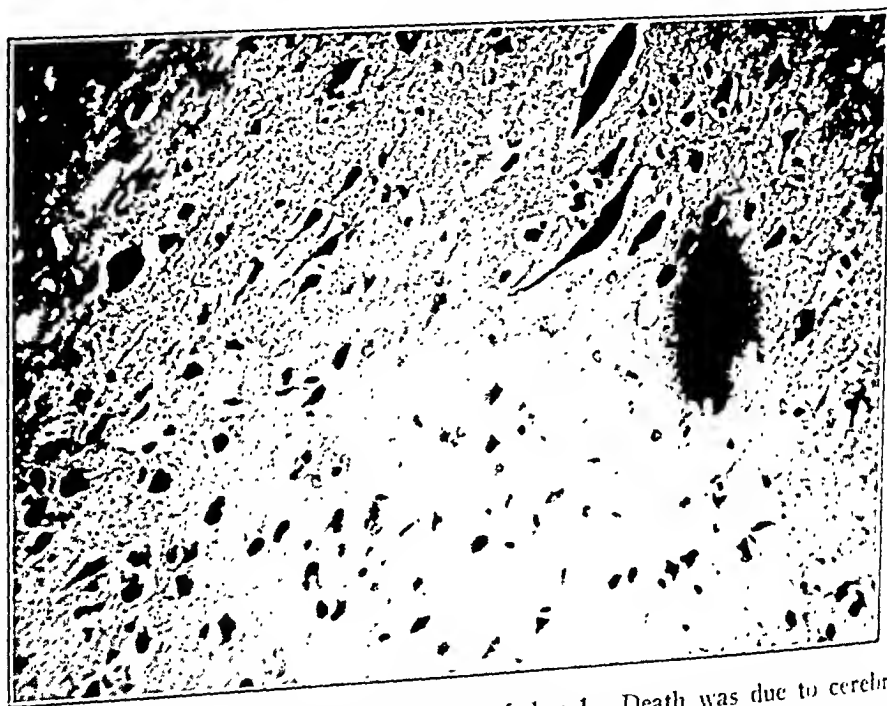


Fig. 4.—Section of the cerebral cortex of dog 1. Death was due to cerebral anoxia. Note the loose, vacuolated stroma, the increased pericellular spaces and the degenerating nerve cells. (Low power.)

edema and mild histotoxic anoxia caused by the preoperative administration of pentobarbital sodium, morphine sulfate and scopolamine hydrobromide.

Animal Experiments.—Anoxic conditions corresponding to those observed in our first patient were repeated on 2 dogs to determine whether similar cerebral changes would develop. Each dog received 2 grains (0.12 Gm.) of pentobarbital sodium intravenously, 35 mg. of procaine hydrochloride intraspinally and nitrogen monoxide and oxygen

6. Landis, E. M.: Micro-Injection Studies of Capillary Permeability. III. The Effect of Lack of Oxygen on the Permeability of the Capillary Wall to Plasma Proteins, *Am. J. Physiol.* 83:528, 1938.

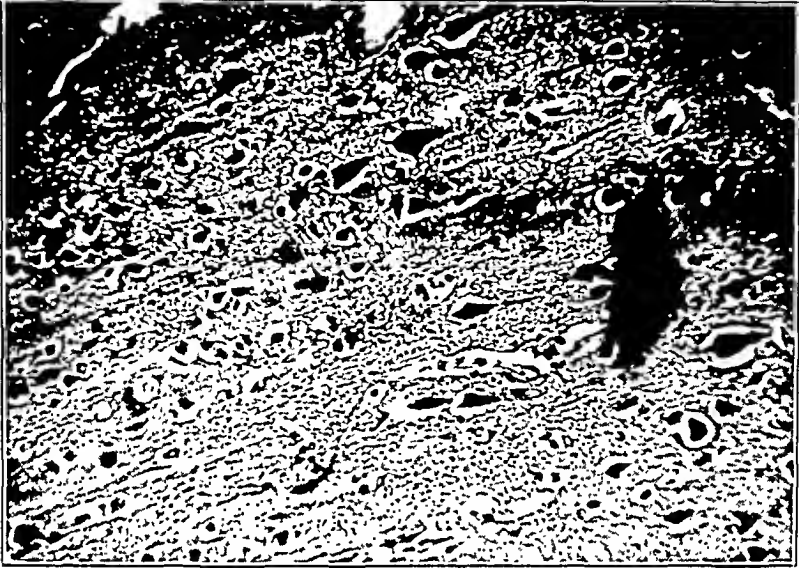


Fig. 5.—Another section of the brain of dog 1. The degenerative changes are typical of anoxia. (Low power.)

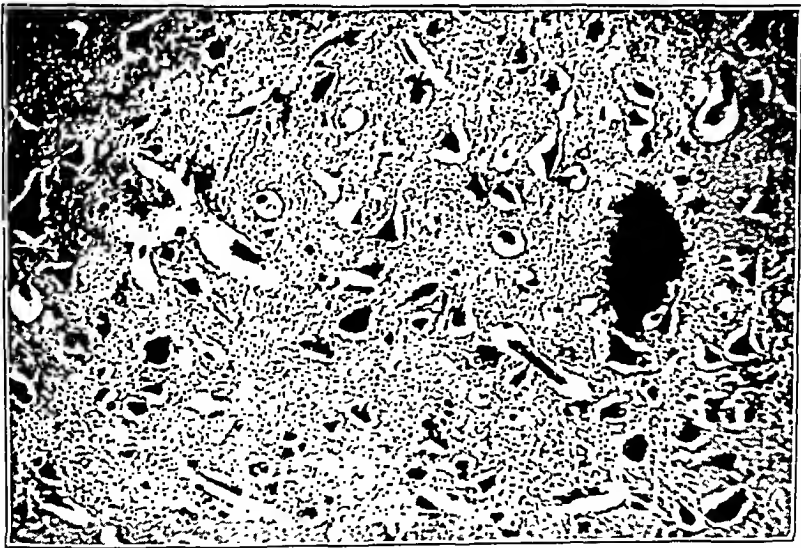


Fig. 6.—Cellular degeneration and increased pericellular and perivascular spaces in a section of the brain of dog 2. (Low power.)

for one hour. A fall in blood pressure to 40 mm. of mercury was produced by trauma to a hindlimb. The spinal anesthetic produced flaccid paralysis of the hind extremities and of the abdomen, but the dogs exhibited running movements with their forelegs. The animals were killed in thirty-six hours, when they were moribund. The brain was fixed in situ by gravimetric instillation of a 10 per cent concentration of solution of formaldehyde U. S. P. through the cannulated carotid arteries. It was then immediately removed, sectioned and again fixed in the solution of formaldehyde.

Histologic sections of the cerebral cortex showed degenerative changes similar to, but milder than, those observed in our patient (figs. 4, 5

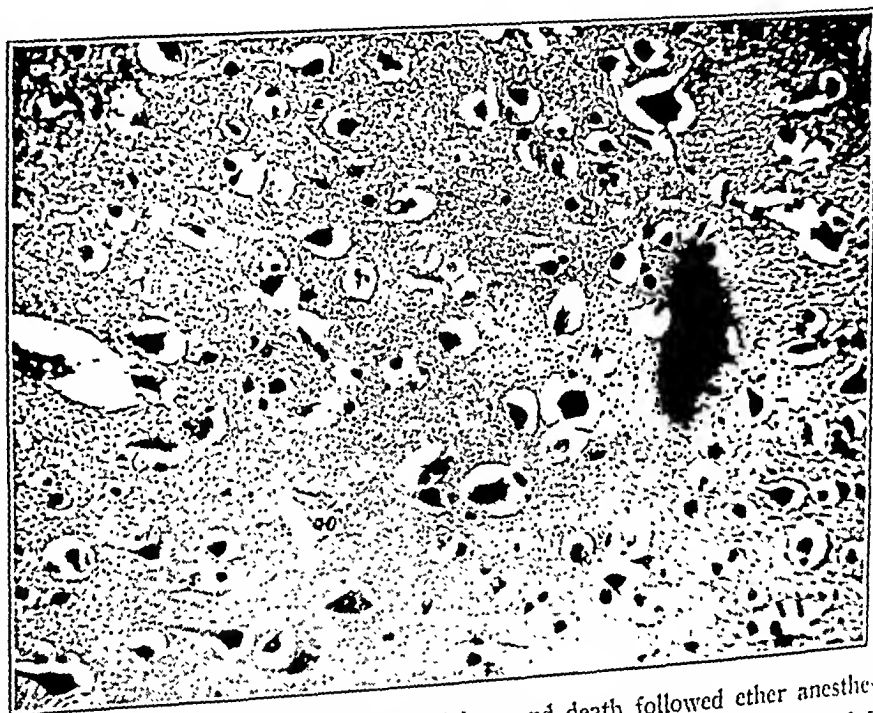


Fig. 7 (case 2).—In this case convulsions and death followed ether anesthesia. There were typical anoxic changes in the brain stem. Note the loose stroma and the increased pericellular and perivascular spaces. Note also the degeneration of the cells. (Low power.)

and 6). The less extensive degenerative changes are probably due to the shorter survival period of the animals and to the absence of anemia.

CASE 2.—A 3 year old white boy had been treated on four previous admissions to the hospital for bilateral clubfoot. On the present admission he was in good general health. The value for hemoglobin was 84 per cent, and the urine was normal. Preoperative medication consisted of $\frac{1}{1000}$ grain (0.1 mg.) of atropine sulfate. Ether anesthesia was maintained over a period of one hour while a bilateral tibial turn was done and a hip spica cast applied. The patient left the operating room apparently in good condition but did not react from the anesthetic for several hours. It was then noticed that he had a lateral head nystagmus, and soon there developed numerous twitchings of the facial muscles. After two hours spasms of the right upper extremity developed, followed by

by generalized convulsions and cyanosis. He was then given a total of 35 grains (2.1 Gm.) of chloral hydrate per rectum over a period of eight hours in an attempt to quiet the spasms, and oxygen and coramine (a 25 per cent solution of pyridine betacarboxylic acid diethylamide) were given to relieve the cyanosis. The respirations became irregular and of the Cheyne-Stokes type. Pulmonary edema developed, and there were numerous rales throughout the chest. The child died from respiratory failure in an oxygen tent fourteen hours after the operation.

Autopsy.—The brain bulged markedly when the dura was incised. On removal it was enlarged and edematous. The choroid plexus and the blood vessels of the brain were congested. Sections through the cortex and brain stem showed vacuolation of the white matter associated with some extravasation of blood into the perivascular spaces and degeneration of the brain cells. Cellular degeneration was most marked in the brain stem (fig. 7). This probably accounts for the early death of the patient from respiratory failure.

Comment.—This patient died from cerebral anoxia incidental to ether anesthesia. The anoxia which caused the restlessness, twitchings and convulsions was made worse by the administration of chloral hydrate. Weber⁷ in 1931 reported a case of a 2 year old boy who had convulsions while under ether anesthesia. This boy lived but was an idiot for the rest of his life. Woolmer and Taylor⁸ reported 4 cases similar to ours in which convulsions and death occurred in the late stages of ether anesthesia. Lundy⁹ made a critical analysis of a series of 145 cases of convulsions under general anesthesia, 13 of which had come under his observation. Ether alone was used in 97 of the cases and was responsible for 17 deaths (17.5 per cent). A wide variety of causes have been ascribed to the convulsions occurring under ether anesthesia in his series. Courville,^{ab} however, has made an excellent review of the subject and reported his studies of 2 cases, and he expressed the belief that the convulsions and death under ether anesthesia are due to anoxemia in some form. The factor of cerebral anoxia resulting in degenerative changes in the brain is apparent in our 2 cases and in our 2 dogs.

Cyanosis was used as a criterion for anoxemia in both of our cases. It should be kept in mind that anoxemia is present long before cyanosis becomes visible and that cyanosis can be present without anoxemia. Lunsgaard and Van Slyke¹⁰ have pointed out that cyanosis depends on the presence of about 5 Gm. of reduced hemoglobin for each hundred cubic centimeters of circulating blood. An anemic patient with less than 5 Gm. of hemoglobin per hundred cubic centimeters of blood cannot

7. Weber, P. F.: Complete Mindlessness (Lowest Degree of Idiocy) and Cerebral (Cortical) Diplegia After Status Convulsivus Associated with Ether Anesthesia, *Brit. J. Child. Dis.* **28**:14, 1931.

8. Woolmer, R. F., and Taylor, S.: Late Ether Convulsions: A Study Based on Four Cases, *Lancet* **1**:1005, 1936.

9. Lundy, J. G.: Convulsions Associated with General Anesthesia, *Surgery* **1**:666, 1937.

10. Lunsgaard, C., and Van Slyke, D. D.: Cyanosis, *Medicine* **2**:1, 1923.

usually become cyanotic until he is moribund. On the other hand, a patient with polycythemia and a hemoglobin content of 19 Gm. may well have 5 Gm. of reduced hemoglobin per hundred cubic centimeters and show cyanosis but not have anoxemia.

SELECTION OF ANESTHETIC

In the selection of an anesthetic the surgeon and the anesthetist are confronted with its anoxic action. We have reviewed the experimental literature pertaining to the anoxic action of the various anesthetics.

Barbiturates.—The barbiturates have been shown to produce various degrees of anoxemia in animals and in patients both in small preoperative doses and in the larger doses which produce surgical anesthesia. One of us (Schnedorf¹¹) found that pentobarbital sodium and sodium amytal in doses of 30 to 35 mg. per kilogram of body weight given intravenously (average total dose for a 10 Kg. dog, 5 grains [0.3 Gm.]) produced an average depression of the arterial blood oxygen saturation from a normal level of 93 per cent to the anesthetic level of 68 and 74 per cent. The depression of blood oxygen was greatest during the first hour but persisted over four hours. A more extensive experimental investigation of the anoxic action of the different anesthetics was reported by McClure, Hartman, Schelling and me.¹² Narcosis in dogs produced by 60 to 70 mg. of evipal (c-c-cyclohexenyl-n-methyl barbiturate) per kilogram of body weight caused a depression of the arterial blood oxygen saturation to 79 per cent; seconal (sodium propylmethylcarbinylallyl barbiturate) (10 to 15 mg. per kilogram) also caused a depression to 79 per cent. Dial narcosis (0.5 cc. per kilogram of body weight) caused a depression to 87.7 per cent in the first hour, and after seven hours the arterial blood oxygen saturation was still depressed (91.4 per cent). Six grains (0.36 Gm.) of seconal given as a preoperative anesthetic produced variations in the blood oxygen ranging from a saturation of 79.7 to 93.5 per cent in the 11 patients studied. Ten grains of cyclopal sodium (the monosodium salt of cyclopentenylallyl barbituric acid) produced a slightly greater depression in some patients. The arterial blood oxygen saturation varied from 74 to 89 per cent in the 7 patients studied. A reduction in blood pressure ranging from 0 to 40 mm. of mercury systolic and 0 to 20 mm. diastolic was observed. The mild anoxemia observed probably resulted from a depression of respiration (anoxic anoxemia) and a fall in blood pres-

11. Schnedorf, J. G.: Oxygen Therapy in Reactions Following Barbiturate Anesthesia and Cisternal Intervention, Surg., Gynec. & Obst. **69**:305, 1939.

12. McClure, R. D.; Hartman, F. W.; Schnedorf, J. G., and Schelling, V.: Anoxia: A Source of Possible Complications in Surgical Anesthesia, Ann. Surg. **110**:835, 1939.

sure (stagnant anoxemia). These workers have also shown by in vivo and in vitro experiments that barbiturates have a direct histiotoxic action and depress the metabolism of the brain tissue. They have found decreased respiration of the brains of dogs anesthetized with pentobarbital sodium by an analysis of the oxygen and carbon dioxide content of the blood from the earotid artery and the jugular vein. Warburg's analysis of the respiration of slices of brain tissue of rabbits narcotized with secenal, pentobarbital sodium, sodium amytal, morphine, evipal and avertin with amylene hydrate showed 12 to 28 per cent decrease in the respiration of the cerebral cortex. Jowett and Quastel¹³ reported depressions of 6 to 32 per cent in the oxidations of dextrose, lactate and pyruvic acid substrates by slices of brain tissue when phenobarbital, chlorbutanol and evipan (evipal soluble) were added. They employed the manometric method of Warburg. Using the same method, Hundhausen¹⁴ has reported a decrease in oxygen consumption by cortical and brain stem tissues of rabbits anesthetized with sodium phenobarbital, chlorbutanol, ethyl carbamate (urethane) and evipal. This action is probably due to a stabilization of the oxyeytochrome of the tissues, so that oxygen is not readily removed, as was shown in the experiments of Keilin.¹⁵

Laidlaw and Kennard¹⁶ reported that after barbiturate anesthesia in cats and in monkeys numerous dilated capillaries are seen in the blood vessels of the hypothalamus. Seevers and Tatum¹⁷ found that the prolonged daily administration of 100 mg. of sodium barbital per kilogram of body weight to 6 dogs resulted in extensive damage to the central nervous system. Capillary dilatation, ring hemorrhages and degeneration of nerve cells were observed in the brain at autopsy.

Nitrogen Monoxide and Oxygen.—The anesthetic effect of nitrogen monoxide is probably due in part to the associated oxygen deficiency. In its early use as an anesthetic it was given without oxygen. As early as 1899, Hewitt¹⁸ ascribed the convulsions and cyanosis preceding a death under nitrogen monoxide anesthesia to anoxemia. The addition of oxygen to the nitrogen monoxide helps to prevent the

13. Jowett, M., and Quastel, J. H.: The Effects of Narcotics on Tissue Oxidations, *Biochem. J.* **31**:565, 1937.

14. Hundhausen, G.: Effect of Cortical and Subcortical Hypnotics on Oxygen Consumption of Surviving Tissue from the Cerebral Cortex and Brain Stem, *Ztschr. f. d. ges. exper. Med.* **102**:477, 1938.

15. Keilin, D.: On Oxyeytochromes: A Respiratory Pigment Common in Animals, Yeast and Higher Plants, *Proc. Roy. Soc., London, s.B* **98**:312, 1925.

16. Laidlaw, A. E., and Kennard, M. A.: Effects of Barbiturate Anesthesia upon the Blood Supply to the Hypothalamus, *Am. J. Physiol.* **129**:650, 1940.

17. Seevers, M. H., and Tatum, A. L.: Chronic Experimental Barbital Poisoning, *J. Pharmacol. & Exper. Therap.* **42**:217, 1931.

18. Hewitt, F.: Death Under Nitrous Oxide, *Lancet* **1**:1053, 1899.

cyanosis but decreases the anesthetic effectiveness. From their studies of oxygen and carbon dioxide in the blood of dogs under nitrogen monoxide anesthesia Leake and Hertzmann¹⁹ concluded that they could not maintain surgical anesthesia without some degree of anoxemia. Green and his associates²⁰ found that a high concentration of nitrogen monoxide was necessary for satisfactory surgical anesthesia in dogs and that this was associated with anoxemia. This action is perhaps best illustrated by Clark (from Sollmann²¹):

Volume Per Cent N ₂ O	O ₂	Depth of Anesthesia	Degree of Asphyxia	Relaxation
80	20	Subconscious analgesia	None	None
86	14	Complete analgesia	None	None
89	11	Partial anesthesia	Slight	Slight
94	6	Complete anesthesia	Dangerous	Partial

McClure and his co-workers¹² reported variations in blood oxygen saturation from 50 to 90 per cent in 20 obstetric patients under nitrogen monoxide and oxygen anesthesia. Most of these patients had had additional preliminary sedation. Raginsky and Bourne²² observed similar variations (48 to 94 per cent saturation) in arterial blood studies of 14 patients under nitrogen monoxide and oxygen anesthesia. The nitrogen monoxide content of the arterial blood in their patients varied from 16.8 to 21.7 volumes per cent. They also found that 80 per cent nitrogen monoxide and 20 per cent oxygen was insufficient in some instances to maintain anesthesia.

Ether.—Ether and oxygen is considered by most anesthetists to be a relatively safe anesthetic. It is, however, not without its dangers and when used in large quantities produces anoxemia. Seventeen deaths occurred in the 97 cases of ether convulsions reviewed by Lundy. Courville^{3b} expressed the belief that convulsions and death under ether anesthesia are due to anoxemia in some form. Jowett and Quastel²³ found that ether may cause an inhibitory effect on the oxidation of dextrose, fructose, lactate and pyruvate by brain tissue slices. Shaw, Steele and Lamb²⁴ reported the results of studies of the blood of dogs

19. Leake, C. D., and Hertzmann, A. B.: Blood Reaction in Ethylene and Nitrous Oxide Anesthesia, *J. A. M. A.* **82**:1162 (April 12) 1924.

20. Greene, C. W., and others: The Distribution of Nitrous Oxide and Oxygen in the Blood of Dogs During Gas Anesthesia, *Arch. Int. Med.* **35**:371 (March) 1925.

21. Sollmann, T.: *Manual of Pharmacology*, ed. 5, Philadelphia, W. B. Saunders Company, 1936.

22. Raginsky, B. B., and Bourne, W.: Blood Oxygen During Nitrous Oxide-Oxygen Anesthesia in Man, *Anesth. & Analg.* **13**:152, 1934.

23. Jowett, M., and Quastel, J. H.: Effects of Ether on Brain Oxidations, *Biochem. J.* **31**:1101, 1937.

24. Shaw, J. L.; Steele, B. F., and Lamb, C. A.: Effect of Ether Anesthesia on Oxygen in Arterial and in Venous Blood, *Arch. Surg.* **35**:1 (July) 1937.

anesthetized with ether. They found a decrease in the oxygen saturation of the arterial blood and concluded that this was indicative of anoxic anoxemia. They also noted an increase in the oxygen capacity of the blood and an increase in the oxygen content of the venous blood. Fuss and Derra²⁵ likewise reported a decrease in the oxygen content of arterial blood during ether anesthesia. In view of these experimental data and of the anoxic degeneration in the brain of our second patient, excessive quantities of this anesthetic should not be used. Oxygen should be administered simultaneously in order to insure a normal oxygen saturation of the arterial blood.

Ethylene.—This gas was introduced as a clinical anesthetic by Luckhardt and Carter²⁶ and by Luckhardt and Lewis²⁷ in 1923. It is not associated with any serious dangers of anoxia. This is because anesthesia can be induced with 90 per cent ethylene and 10 per cent oxygen. After the induction satisfactory surgical relaxation may be maintained with 80 per cent ethylene and 20 per cent oxygen. Only 1 patient of the 10 reported on in the studies of McClure and his co-workers¹² had a reduction in the arterial blood oxygen saturation below the level expected in view of the preoperative medication with barbiturates and morphine sulfate.

Cyclopropane.—Lucas and Henderson²⁸ advocated cyclopropane as an anesthetic in 1929. Satisfactory surgical anesthesia can be maintained with mixtures of 25 per cent cyclopropane and 75 per cent oxygen (Sollmann²¹). Analysis of the gaseous content of the arterial blood of 6 patients showed only a slight depression of oxygen in 4, while the rest had a normal arterial blood oxygen saturation despite the fact that all of them had had morphine or seconal (McClure and others).

Avertin with Amylene Hydrate.—Avertin with amylene hydrate is frequently used rectally in small doses (50 to 100 mg. of tribromethanol per kilogram of body weight) as a basal anesthetic. Although it is safe in doses up to 150 mg. of tribromethanol per kilogram its use in large doses for purposes of complete anesthesia should be discouraged. Kennedy²⁹ and Greer³⁰ showed that vasodilatation and a sharp depres-

25. Fuss, H., and Derra, E.: Decreased Oxygen Content of Arterial Blood During Ether Anesthesia, *Arch. f. exper. Path. u. Pharmacol.* **156**:64, 1930.

26. Luckhardt, A. B., and Carter, J. B.: Physiologic Effects of Ethylene, *J. A. M. A.* **80**:765 (March 17) 1923.

27. Luckhardt, A. B., and Lewis, D.: Clinical Experiences with Ethylene-Oxygen Anesthesia, *J. A. M. A.* **81**:1851 (Dec. 1) 1923.

28. Lucas, G. H. W., and Henderson, V. E.: New Anesthetic Gas: Cyclopropane; Preliminary Report, *Canad. M. A. J.* **21**:173, 1929.

29. Kennedy, W. P.: Preliminary Note on the Blood Pressure During Avertin Anesthesia, *Tr. Med.-Chir. Soc. Edinburgh*, 1929-1930, p. 142; in *Edinburgh M. J.* September 1930.

30. Greer, C. C.: Rectal Narcosis with Avertin, *West Virginia M. J.* **26**:538, 1930.

sion in blood pressure may be observed about eight minutes after its administration. There have been noted also an associated decrease in the blood volume and a depression of the heart. McClure and his associates³² have reported an average blood oxygen saturation of 83 per cent in 6 dogs narcotized with surgical doses of avertin with amylene hydrate (180 mg. of tribromethanol per kilogram of body weight). Smaller doses (70 to 90 mg. per kilogram) given to 10 patients depressed the oxygen saturation 3 to 20 per cent below normal, and the blood pressures showed a consistent fall, ranging from 4 to 62 mm. of mercury. Derra and Korth³¹ also reported a 3 to 6 per cent depression of the arterial and venous blood oxygen saturation in 9 dogs under large doses of avertin with amylene hydrate (5 Gm. of tribromethanol per kilogram).

Spinal Anesthesia.—Many surgeons find spinal anesthesia to be the ideal form of anesthesia where it is applicable. It affords complete relaxation without loss of consciousness. Spinocaine (a solution of procaine hydrochloride, amyloprolanine, ethyl alcohol and strychnine sulfate) in 1 to 3 cc. doses or procaine hydrochloride in 35 to 50 mg. doses is adequate for operations below the umbilicus. Nupercaine hydrochloride in doses of 12 to 17 cc. provides adequate relaxation for operations on the stomach, the gallbladder and the upper part of the abdominal region. Analysis of the arterial blood of 10 patients under spinocaine anesthesia showed that as long as no depression of blood pressure was obtained the blood oxygen saturation remained normal. In 2 instances in which the blood pressure fell 40 to 60 mm. of mercury the oxygen saturation also was low (83 and 85 per cent [McClure and others]). Shaw and his associates³² reported an increase in the oxygen saturation of the arterial blood and a decrease in the oxygen saturation of the venous blood. They regarded the increased arteriovenous difference as indicative of mild stagnant anoxemia. As a result of experiments on 5 cats, Bradshaw³³ concluded that a fall in blood pressure following spinal injection of procaine hydrochloride is due to paralysis of the vasomotor nerve fibers. Since no further fall in blood pressure occurred with anesthesia above the fifth thoracic and below the seventh cervical segment, he concluded that the vasoconstrictor fibers from the fifth thoracic level down are the important fibers in the most common type of blood pressure reaction occurring under

31. Derra, E., and Korth, J.: Influence of Carbon-Dioxide Inhalation on Gas Exchange in Tri-Brom-Ethanol (Avertin) Anesthesia, *Beitr. z. klin. Chir.* **171**:53, 1940.

32. Shaw, J. L.; Steele, B. F., and Lamb, C. A.: Effect of Spinal Anesthesia on Oxygen in Arterial and Venous Blood, *Arch. Surg.* **35**:503 (Sept.) 1937.

33. Bradshaw, H. H.: The Fall in Blood Pressure During Spinal Anesthesia, *Ann. Surg.* **104**:41, 1936.

spinal anesthesia. Doud and Rovenstine³⁴ reported a 47 per cent increase in the circulating time when spinal anesthesia extended below this level. Burch and Harrison³⁵ determined the cardiac output in dogs by the Fick principle. Spinal anesthesia induced by procaine hydrochloride resulted in a diminished cardiac output which was secondary and subsequent to the fall in blood pressure.

These experimental reports indicate that anoxemia is not a factor in spinal anesthesia as long as the blood pressure is maintained. This can best be done by avoiding unnecessarily large doses of the spinal anesthetic. In addition, prophylactic doses of 5 mg. of neo-synephrin hydrochloride, $\frac{3}{4}$ grain (0.045 Gm.) of ephedrine sulfate, 1 cc. of epinephrine (1:2,000) in oil or $\frac{3}{4}$ grain 0.045 Gm.) of ephedrine sulfate and 0.5 cc. of solution of posterior pituitary given intramuscularly may be used before the spinal anesthetic is given. Additional doses should be given throughout the course of the anesthesia if the blood pressure fails. In such instances inhalations of high concentrations of oxygen are indicated. The use of spinal anesthesia for operations on the head and neck as advocated by Koster and Kasman³⁶ is not advisable, because it depends on the selective paralysis of the sensory to the motor nerves. Although the anoxemia following paralysis of the intercostal nerves may be mild, the interference with respiration on paralysis of the phrenic nerves (fourth, fifth and sixth cervical segments) may produce severe anoxemia.

ANOXIA IN SHOCK

In addition to the anoxic action of the anesthetic, the surgeon has to contend with the anoxic effects of surgical and of traumatic shock. Munslow, Crawford, McClure and one of us (Schnedorf)³⁷ have reported depressions of arterial blood oxygen saturation from 5 to 44 per cent below normal in 9 dogs and in 12 patients with injuries to the head. Oxygen therapy restored the blood oxygen saturation to and above normal. Orr and one of us (Schnedorf)³⁸ investigated the

34. Doud, E. A., and Rovenstine, E. A.: Changes in the Velocity of the Blood Flow During Spinal Anesthesia, *Anesthesiology* **1**:82, 1940.

35. Burch, J. C., and Harrison, T. R.: Effect of Spinal Anesthesia on Cardiac Output, *Arch. Surg.* **21**:330 (Aug.) 1930.

36. Koster, H., and Kasman, L. P.: Spinal Anesthesia for the Head, Neck and Thorax: Its Relation to Respiratory Paralysis, *Surg., Gynec. & Obst.* **49**:617, 1929.

37. Schnedorf, J. G.; Munslow, R. A.; Crawford, A. S., and McClure, R. D.: Anoxia and Oxygen Therapy in Head Injury, *Surg., Gynec. & Obst.* **70**:628, 1940.

38. Schnedorf, J. G., and Orr, T. G.: I. The Beneficial Effects of Oxygen Therapy in Experimental Traumatic Shock, *Surg., Gynec. & Obst.* **73**:79 (July) 1941; II. The Beneficial Effects of Oxygen Therapy in Experimental Histamine Shock; III. Oxygen Therapy in Shock Due to Hemorrhage, *ibid.*, to be published.

value of oxygen therapy in cases of traumatic and histamine shock and in cases of shock produced by hemorrhage in more than 60 dogs. There were noted a decrease in the oxygen content and saturation of the blood from the femoral artery and vein of dogs in traumatic shock anesthetized with pentobarbital sodium. Oxygen therapy caused a 70 per cent increase in the length of life of dogs in traumatic shock, a 71 per cent increase in the duration of life of dogs in histamine shock and a 17 per cent increase in the length of life of dogs in shock due to hemorrhage. In addition, the last-mentioned dogs, which received oxygen, withstood the loss of larger volumes of blood. The oxygen therapy was less effective in prolonging the life of this group because of the loss of oxygen-carrying hemoglobin.

Aub and Cunningham³⁹ also reported that traumatic shock in cats under ethyl carbamate (urethane) anesthesia caused a marked slowing of the blood flow and a decrease in the oxygen content of the venous blood from an average of 12.3 to 4.8 volumes per cent. A reduction in the oxygen content of the arterial blood (from 17.2 to 12.8 volumes per cent) was also noted by them.

Wood, Mason and Blalock⁴⁰ reported a depression in blood oxygen of anesthetized dogs in traumatic shock, in histamine shock and in shock due to hemorrhage. Even fifteen minutes of oxygen therapy had a beneficial effect on the blood pressure, pulse and respiration of their dogs.

TREATMENT OF ANOXIA

On the basis of the experimental evidence just reviewed, certain conclusions are justified regarding the treatment of anoxia in the surgical patient. Anoxemia can best be treated by prevention. The hemoglobin level of every patient to be operated on should be checked. Anemic anoxemia should be prevented by adequate preoperative treatment and blood transfusions. The hemostasis and the operative technic should be such as to prevent unnecessary loss of large quantities of blood and the development of shock at the time of operation. In extensive operations, such as radical amputations of the breast, stomach and colon, 600 to 1,000 cc. of blood should be given during the operation. This procedure is used routinely in some clinics.

Even with an effective level of blood hemoglobin maintained, the surgeon and the anethetist must exercise care in the selection of the preoperative sedatives. In many instances verbal reassurance by the surgeon is far better than small doses of barbiturates in allaying the

39. Aub, J. C., and Cunningham, T. D.: Studies in Experimental Traumatic Shock: II. The Oxygen Content of the Blood, *Am. J. Physiol.* **54**:408, 1920.

40. Wood, G. O.; Mason, M. F., and Blalock, A.: Studies on the Effects of Inhalation of a High Concentration of Oxygen in Experimental Shock, *Surgery* **8**:247, 1940.

fears of the patient. If barbiturates are used, only small doses should be given. After the rectal administration of avertin with amylene hydrate as a basal anesthetic the patient must be watched closely.

Finally, the selection of a suitable anesthetic should be made. From the standpoint of anoxemia only the degree of anesthesia necessary to perform the operation painlessly should be used, and those anesthetic agents which do not produce anoxemia should be given preference. Oxygen should be used in combination with the anesthetics which are known to produce mild or severe anoxemia. Should anoxemia and shock develop, a moderate Trendelenburg position, inhalations of high concentrations of oxygen, artificial respiration and cardiac and respiratory stimulants should be given. Neo-synephrin and epinephrine are of great value in restoring the blood pressure, but subsequent precautions should be taken not to overload the system with intravenous fluids, because of the transient anuria produced by these drugs. It should be remembered that oxygen therapy is indicated long before cyanosis is present and long after it has disappeared.

SUMMARY

The importance of anoxemia in surgery and anesthesia is emphasized.

Two cases of anesthetic death due to anoxemia are presented and analyzed. The anoxic degenerative changes in the brains of the patients are demonstrated. Degenerative changes in the brains of 2 dogs subjected to the same anesthetics and the same type of shock to which 1 of our patients had been subjected are also demonstrated.

The experimental literature relative to the anoxic effect of the various anesthetics is reviewed.

The importance of shock in the production of anoxemia and the beneficial action of inhalations of high concentrations of oxygen in cases of shock are emphasized.

The principles of the treatment of anoxemia in surgery and anesthesia are outlined.

EARLY CARCINOMA OF THE COLON

I. NATURE AND ADEQUATE TREATMENT OF SMALL CARCINOMAS

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The study reported here is concerned with the diagnosis, treatment and end results of 61 colonic carcinomas less than 2.5 cm. in diameter. The patients were examined and treated at the Mayo Clinic during the years 1909 to 1934 inclusive. This investigation was prompted by a discussion of the advisability of extensive and radical resection for such small lesions. The lesions varied from 0.5 to 2.5 cm. in diameter, the average being about 1 cm.; lesions of no one size predominated. Pedunculated polypoid growths and carcinomas arising in association with multiple polyposis were not considered in this series.

Thirty-four of the 61 patients were women and 27 were men. The youngest was 30 years of age and the oldest 75; the average age was 54 years. The average duration of symptoms was eight months and three weeks; the longest was three years and the shortest three weeks.

Although the lesions were small, 11 of the 14 which developed above the sigmoid flexure caused obstruction; only 3, however, caused bleeding. Of 11 which were within reach of the sigmoidoscope but above the reach of the finger, bleeding was the prominent symptom with 7; change of bowel habits was noted with 3, and 1 caused no subjective or objective symptoms. All lesions in the entire series which were found to be more than 10 cm. above the anal canal were reported as not palpable by digital examination. Several of the 36 growths that were within reach of the examining finger caused more than one symptom. Bleeding occurred with 30 of these 36 growths and change of bowel habits with 14; with 1 there were no symptoms.

Twenty-six of the 61 lesions were situated within approximately 5 cm. of the anus. Fourteen of these were situated on the anterior wall of the rectum; 5, on a lateral wall, and 7, on the posterior wall.

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Ten of the 61 lesions were located 5 to 10 cm. above the anus. Six of these were on the anterior wall; 1, on a lateral wall, and 3, on the posterior wall. For 11 lesions that were situated between 10 and 25 cm. above the anus, designation of the actual location was difficult. Fourteen others of the 61 lesions were proximal to a point 25 cm. above the anus.

The five year survival rates in relation to the grade of malignancy of the lesions (Broders' classification) are shown in table 1. In general, the survival rate decreased as the grade of malignancy increased.

TABLE 1.—*Five Year Survival According to Grade of Malignancy*

Lesion, Grade	Patients	Lived 5 Years or More After Operation		Recurrence of Carcinoma More Than 5 Years After Operation
		Number	Per Cent	
1.....	14	10	71	1
2.....	34	14	41	2
3.....	10	3	30	0
4.....	3	1	33	1
Total.....	61	28	46	4

TABLE 2.—*Five Year Survival According to Invasion of Bowel (Dukes's Classification)*

Type	Patients	Lived 5 Years or More After Operation		Recurrence of Carcinoma More Than 5 Years After Operation
		Number	Per Cent	
A *.....	34	21	62	2
B †.....	14	2	14	0
C ‡.....	9	4	44	2
Liver.....	4	1	25	0
Total.....	61	28	46	4

* Growth is limited to wall of intestine.

† Growth has extended into the extrarectal tissues.

‡ Growth has spread to adjacent lymph nodes.

The 61 tumors were considered from the standpoint of invasion of the intestinal wall according to Dukes's classification (table 2). Thirty-four of the 61 showed no extramural spread, and 21 of the 34 patients lived five years or more after operation. However, 27 tumors spread extramurally, and with 14 of the 27 there was local invasion beyond the intestinal wall. Only 2 of the 14 patients lived five or more years after operation. Of the 27 patients whose tumors showed extramural spread, the lymph nodes were involved in 9; 4 of the 9 lived five years or more after operation. Four of the 27 patients had hepatic involvement; 1 of these lived at least five years after operation.

When it is considered that the growths were less than 2.5 cm. in diameter, the question may arise why the end results were not better.

Accordingly, the data were reviewed carefully in order to determine what therapeutic measures had been instituted. The lesions were grouped on the basis of location.

A lesion in the ascending colon was removed by local cautery excision. One in the hepatic flexure was treated by ileocolostomy and right hemicolectomy. A Mikulicz operation was employed to remove a lesion of the transverse colon. Of the 11 lesions which were above the proctoscopic field in the left part of the colon, 6 were treated by a Mikulicz procedure, 1 by colostomy and Mikulicz resection and 4 by extraperitoneal resection. Of the 11 lesions which were within reach of the proctoscope but beyond the reach of the examining finger, 1 was treated by colostomy and extraperitoneal resection, 1 by combined abdominoperineal resection and 1 by transcolonic excision. Three were handled by an extraperitoneal operation and 5 by colostomy followed by anterior resection. Of 36 lesions within reach of the examining finger, 16 were treated by colostomy and posterior resection; 6 were treated by resection with establishment of a sacral anus; 5 were treated by excision with restoration of continuity of the bowel; 2 were considered suitable for combined abdominoperineal resection; 5 were eradicated by local cautery excision, and 2 were eradicated by fulguration.

It appears from these data that the operations performed were as radical as those commonly employed in surgical treatment of lesions much larger than the average size of the lesions in our group. Analysis of results based on the methods of treatment revealed nothing encouraging. The patient who had been subjected to resection and ileocolostomy died subsequently of malignant disease of the colon. Seven of 8 patients who had been subjected to a Mikulicz type of operation died subsequently of carcinoma of the colon. Of 8 patients who underwent extraperitoneal resection, 4 died subsequently of carcinoma of the colon.

Four of the 5 patients who were subjected to colostomy and anterior resection died later of colonic malignant disease. Six of the 16 patients who were subjected to posterior resection died subsequently of carcinoma of the colon. Of 5 patients, whose lesions were excised locally with subsequent restoration of the continuity of the intestine, 1 died later of carcinoma of the colon. Of the 6 patients whose carcinomas were locally excised by cautery, 1 died later of colonic carcinoma. Of the 6 patients treated by excision with establishment of a sacral anus, 4 died of colonic carcinoma. Two patients whose lesions had been fulgurated were alive at the end of five years, and the 3 patients who had been subjected to the combined abdominoperineal resection were also alive at the end of five years.

Of the 61 patients 28 were living at the end of five years after treatment; 24 of these were free of carcinoma at the time of investigation. Five of the 61 patients died immediately after operation.

COMMENT

The small size of the lesions in this group was not a prominent factor in determining the ultimate result as far as cure or further development of carcinoma was concerned, nor did the type of surgical procedure used for any individual growth constitute the determining factor in the ultimate result. The sites of the lesions, their grade of malignancy (Broders' classification) and their types according to infiltration of the wall, extramural spread, involvement of the lymph nodes (Dukes's classification) and age of the patients at onset seemed to be vital prognostic factors.

Although the primary intention in this study was to ascertain the ultimate results obtained by surgical treatment of small carcinomas of the colon, analysis of the records has brought forth several interesting facts. It may seem surprising that 11 of the patients whose lesions were situated cephalad to the sigmoid portion of the colon should have symptoms of obstruction. The probable explanation for this is that in each of these patients obstruction of the large intestine was caused by intussusception initiated by the presence of tumor and augmented by peristalsis. This phenomenon is seen commonly in association with carcinoma of the colon and accounts for the not infrequent history of recurrent episodes of intestinal obstruction relieved at first by conservative measures but culminating in complete intestinal obstruction and making surgical intervention imperative. The infrequency of rectal bleeding with this group of tumors is remarkable and emphasizes the fact that an apparently simple stomach ache may be the only sign of carcinoma and that the physician must ever be alert to adjudge such a symptom carefully. The youth of some of the patients hardly requires emphasis, for it is well known that carcinoma is not confined to persons in the later decades of life.

From the diagnostic standpoint it is significant that none of the lesions which were situated more than 10 cm. above the anus were palpable by digital examination. (It is commonly believed and taught that if the patient is placed in an advantageous position any growth situated within the rectum, which is approximately 15 cm. long, can be palpated. Although it is probably true that a larger lesion will tend by means of its weight to prolapse toward the anus and thus come within reach of the examining finger, a smaller lesion will remain in its original position. A lesion situated more than 10 cm. above the anus will be beyond the reach of the average index finger.)

The final results were discouraging. A ray of hope appeared when we found that carcinoma did not occur subsequently in patients in whom the growth had been situated on a lateral wall of the rectum, but there

were too few of these patients to allow us to announce the discovery of a zone of minimal malignancy. Further work is needed to investigate this possibility.

The prognosis in relation to the individual lesions was made on the basis of Broders', MacCarty's¹ or Dukes's method of grading malignancy and was generally sustained. If the pedunculated growths and the lesions associated with polyps in other parts of the colon had been included in this series, probably we should have found a higher proportion of the lower grades of malignant growths. The presence of metastatic lesions in the lymph nodes in some of our patients bears out the contention of McVay,² who stated that there is no relation between the size of the lesion and the extent of metastatic involvement. The occurrence of hepatic involvement can be comprehended readily if it is realized that this represents an embolic accident caused by invasion of a vein by neoplasm. This can occur at any stage in the development of a malignant tumor. Although the unfavorable results with growths which had exceeded the circumscribed boundaries of the parental tissue served only to confirm our impression that the prognosis for tumors of this type is not favorable, the number of carcinomas which developed where there had not been extramural spread was somewhat unexpected. Rankin and Broders,³ in considering factors influencing the prognosis of rectal carcinomas, stated that if metastatic lesions are absent the grade of malignancy is not as important as otherwise. The occurrence of new growths after apparently complete surgical ablation suggests that the causative factor may reside not in the epithelial cells of the growth itself but in the surrounding tissue. MacCarty has stressed the significance of the environmental relations of various cells in the production of carcinoma and has drawn particular attention to the influence of lymphoid tissue on the nutrition of epithelial cells. Perhaps wide resection is necessary to cure. Coffey and one of us (J. A. B.)⁴ emphasized recently the association of large lymph follicles in the submucosa with polyps of the colon, and in the same article the belief was expressed that the lymph follicles may play a part in the causation of certain types of polypoid hyperplasia. In the cases on which this study is based we were able to demonstrate changes of this type in the tissue surrounding the carcinomas, and, believing that this might be the factor responsible

1. MacCarty, W. C.: The Genesis of Cancer, Proc. Staff Meet., Mayo Clin. **12**:295-297 (May 12) 1937.

2. McVay, J. R.: Involvement of the Lymph-Nodes in Carcinoma of the Rectum, Ann. Surg. **76**:755-767 (Dec.) 1922.

3. Rankin, F. W., and Broders, A. C.: Factors Influencing Prognosis in Carcinoma of the Rectum, Surg., Gynec. & Obst. **46**:660-667 (May) 1928.

4. Coffey, R. J., and Bagen, J. A.: Intestinal Polyps: Pathogenesis and Relation to Malignancy, Surg., Gynec. & Obst. **69**:136-145 (Aug.) 1939.

for some of the recurrent carcinomas, we carried out a detailed histologic study of this tissue. In every instance the results suggested the pathogenesis of at least some types of new growths ending in polypoid epithelial hyperplasia. The significance of tissue changes in the intestinal wall adjacent to these neoplasms cannot be overrated. They make it apparent that in many cases one is not dealing with recurrence of a removed carcinoma but that a new carcinoma, separate and distinct from the original growth, has caused death. This probably is the cause of so-called recurrent carcinoma in cases in which the lesion has been completely eradicated. A comprehensive study of these tissue changes will be detailed in a subsequent paper.

The immediate results of surgical treatment of these cancers were entirely satisfactory. There was no subsequent treatment, which brings up the question of the possibility and advisability of such treatment. There may not be logical or even reasonable postoperative treatment at hand, but the possibilities of such treatment should be explored, to the end that something may be done to cope with the possibility that carcinoma may occur in carcinoma-bearing tissue adjacent to the lesion removed.

EARLY CARCINOMA OF THE COLON

II. RELATION BETWEEN SUBCLINICAL INFLAMMATORY PROCESSES AND CARCINOMA

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It is now generally agreed that a cancer represents the ultimate phase of a definite series of changes rather than a mere fortuitous incident in the life of the tissues, and, although the nature of these changes is not yet completely understood, it is known that they result from developmental change, from reaction to prolonged irritation or from unsuccessful attempts at tissue repair. Evidence giving support to this has been accumulated by investigators in three separate fields—experimental workers, pathologists and clinicians.

EXPERIMENTAL WORK

Experiments have been carried out chiefly on the so-called tar cancer in mice. Cramer,¹ by applying one of the known carcinogenic substances to the skin of mice, was able to produce typical epithelioma in these animals. He observed that the process is not continuous but is composed of two phases: (*a*) a process of long duration inducing in the cells a condition of "potential" malignancy which is kept in check by the other tissue elements and (*b*) a local breaking down of this resistance which allows immediate malignant transformation of the potentially malignant cells. He emphasized that the factors governing the local onset of malignancy do not reside in the epithelial cells but seem to be attributable to the activity of the mesenchymal cell system. Kreyberg² has added confirmation to this belief by demonstrating a reaction in the subepithelial connective tissue which consists of hyperemia and leukocytic infiltration

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1. Cramer, W.: On Experimental Carcinogenesis: The Local Resistance of the Skin to the Development of Malignancy, *Brit. J. Exper. Path.* **10**:335-346 (Oct.) 1929.

2. Kreyberg, L.: Ueber präcanceröse Gefässveränderungen, *Virchows Arch. f. path. Anat.* **273**:367-440 (Sept. 6) 1929.

followed by fibrosis. This typical inflammatory response precedes any recognizable alteration in the epithelial cells. The work of Murray³ and Cramer⁴ has further established that a fully developed cancer exhibits certain biologic characteristics. While the cancer continues to increase by autoplasty and to spread by metastatic growth, in the rest of the potentially malignant region, which may be large, no further malignant growth develops. This is due to inhibitory influences exerted on the tissues by the presence of the cancer, and the phenomenon has been designated "secondary resistance" to distinguish it from the local, or "primary," resistance which checks the development of the initial malignant growth. Murray's experiments show that after one growth has become established the induction of a second primary growth meets with intense resistance and that the tissues apparently are unable to react with cancerous proliferation to procedures which initiate it with certainty in other animals. The removal of the primary tumor causes the resistance also to be removed, and Cramer found that in mice in which the growth has been excised, the rest of the potentially malignant region being left in situ, a second primary cancer develops in some other part of the potentially malignant region, although sometimes as long as six months may elapse between the removal of the first and the appearance of the second neoplasm. (This period corresponds biologically to fifteen years of the life of man and is therefore a factor to be considered in evaluating the usual criterion of clinical cure of cancer, which is arrest for five or, at the most, ten years.) It is to be noted that all these observations have been made on cutaneous cancer, and, although Thomas⁵ has described a technic by which the experiments can be repeated by using the large intestine instead of the skin, he has not yet made any report of the results of this procedure.

PATHOLOGIC PICTURE IN MAN

The relation of gastric ulcer to cancer of the stomach has been adequately demonstrated by MacCarty,⁶ and, more recently, Robertson⁷

3. Murray, J. A.: Primary and Secondary Resistance to the Induction of Cancer, *Scient. Rep. Invest. Imp. Cancer Research Fund* 8:75-84, 1923.

4. Cramer, W.: Resistance and Susceptibility to Cancer, in Adair, F. E.: *Cancer: International Contributions to the Study of Cancer in Honor of James Ewing*, Philadelphia, J. B. Lippincott Company, 1931, pp. 20-29.

5. Thomas, F.: La technique de l'anus contre nature abdominal et de l'introduction de substances carcénigènes dans un segment colique isolé, chez le rat, *Compt. rend. Soc. de biol.* 118:384-386, 1935.

6. MacCarty, W. C.: Chronic Gastric Ulcer and Gastric Carcinoma: A Study of Five Hundred and Seven Simple Chronic Ulcers and Eight Hundred and Ninety-Five Carcinomatous Ulcers, *Am. J. Roentgenol.* 7:591-596 (Dec.) 1920.

7. Robertson, H. E.: Ulcerative Gastritis and Residual Lesions, *J. A. M. A.* 112:22-27 (Jan. 7) 1939.

has commented on the frequency with which inflammatory changes are found in the gastric mucosa in association with cancer. In the large intestine, however, although it has been observed that cancer tends to occur with greater frequency in the presence of certain pathologic conditions, such as familial polyposis and chronic ulcerative colitis, frequently a malignant growth arises in mucous membrane when no previous lesion has been suspected or demonstrated. Cain and Bensaude,⁸ after examining the structure of a series of small cancers, concluded that such growths can be divided into two groups, those arising in adenomatous tissue and those occurring in apparently healthy mucous membrane. Dukes⁹ made a careful study of the mucous membrane surrounding cancer of the large intestine and stated that in this tissue there are localized patches of hyperplasia discoverable only with the microscope. He expressed the opinion that adenoma represents a more advanced stage of this hyperplasia which has necessitated an architectural modification in the normal relation of epithelium to connective tissue in order that the greater number of secreting cells may be supported and adequately nourished. He suggested that the development of a cancer of the colon can be traced through a series of stages, starting with the development of patches of epithelial hyperplasia which extend over a large stretch of the bowel. As the hyperplasia continues, a crop of sessile adenomas is found in this region. Sooner or later a cancer arises either in one of these adenomas or in the neighboring epithelium. This hypothesis postulates a potentially malignant state existing in the epithelium prior to the development of the actual cancer, but Dukes made it clear that the process of carcinogenesis may become arrested at any stage by sudden retrogression of the hyperplasia or by pedunculation and shedding of the multiple adenomas and therefore may fail to reach its destined goal of malignancy. The conception of a potentially malignant state has received support from the observations of several pathologists and has been described under a variety of names. The condition has been studied extensively in the breast, and on the basis of its morphologic appearances it has been referred to as "mazopathia" by Cheatle¹⁰ and as "epitheliosis" by Dawson.¹¹ Cytologic studies by MacCarty¹² have

8. Cain, A., and Bensaude, A.: *Les modes d'apparition du cancer du rectum; considérations tirées de l'étude des petits cancers*, Arch. d. mal. de l'app. digestif **27**:353-374 (April) 1937.

9. Dukes, C.: *Simple Tumours of the Large Intestine and Their Relation to Cancer*, Brit. J. Surg. **13**:720-733, 1926.

10. Cheatle, G. L.: *Precancerous Conditions of the Breast*, Cancer Rev. **5**:81-95 (Feb.) 1930.

11. Dawson, E. K.: *A Histological Study of the Normal Mamma in Relation to Tumour Growth*, Edinburgh M. J. **41**:653-682 (Dec.) 1934.

12. MacCarty, W. C.: *Cancer's Place in General Biology*, Am. Naturalist **52**:395-408 (Aug.-Sept.) 1918.

revealed certain changes in the essential structure of the nuclei of individual cells which establish their potential malignant pathogenicity. These changes he called "secondary cytoplasmia." Each terminology, however, embodies the fundamental conception of the potentially malignant state.

CLINICAL OBSERVATIONS

Clinical support for the existence of a potentially malignant state is less readily available. While it is sometimes possible to obtain a history of intestinal dysfunction immediately preceding the appearance of a rectal cancer, as was suggested by Miles,¹³ more often this story is completely lacking, a fact which has led Horder¹⁴ to condemn such a history as "pure supposition." Gordon-Watson¹⁵ has proposed that in routine sigmoidoscopic examination a magnifying lens should be used to search for the minute adenomas described by Dukes, but we have no record of the success of this undertaking. The relation of fully developed adenoma to cancer is widely recognized, but readily visible or palpable adenomas are found in only a small proportion of cases of cancer of the colon. In summarizing this evidence we may say that, while available data indicate that a potentially malignant region exists in the colon prior to and coincident with the development of malignancy, they do not demonstrate the nature and extent of the potentially malignant region with sufficient accuracy to enable it to be recognized and treated by the clinician.

ORIGINAL OBSERVATIONS

In reviewing the results obtained by surgical treatment in a series of small cancers of the colon we were impressed by the high proportion of instances in which the lesion recurred locally after the growth had apparently been eradicated to the entire satisfaction of both the surgeon and the pathologist. Three explanations might be suggested to account for such a recurrent lesion: 1. The primary growth may have been incompletely removed, and malignant tissue may inadvertently have been left behind. 2. Errors in surgical technic may have allowed cancer cells to become implanted or inoculated in the edges of the wound. 3. The so-called local recurrence may represent a second primary growth arising in the epithelium at some distance from the original neoplasm. From our material we were able to select 30 specimens with regard to which the possibility of incomplete removal or accidental inoculation could be eliminated. These were small lesions measuring less than an inch (2.5 cm.) in diameter with which there had been no evidence of metastatic

13. Miles, W. E.: *Cancer of the Rectum*, London, Harrison & Sons, 1926.

14. Horder, T.: *Medical Notes*, London, Oxford University Press, 1921.

15. Gordon-Watson, C.: *The Etiology of Rectal Tumours in Relation to Treatment*, *Practitioner* **126**:481-494 (May) 1931.

or extramural spread at the time of operation and the removal of the growth had ablated a considerable portion of the surrounding tissue. Careful histologic examination of the excised surgical specimens showed that in each case the cancer had been removed in its entirety. Furthermore, as in each instance the lesion was small and situated at some distance from the point of section of the bowel, little handling had been necessary at the time of operation, and so the likelihood of local inoculation did not exist. We felt justified, therefore, in assuming that any "recurrence" which took place in this series must represent a second primary neoplasm. The theory of the second primary growth was given prominence by Michelson¹⁶ some fifty years ago. More recently the observations of Gordon-Watson, which attempt to correlate the phenomenon of recurrence with the existence of a potentially malignant region, have awakened new interest in this aspect of cancer, and Thompson,¹⁷ in discussing a growth which appeared to be a "brand new tumour" arising at the site where a previous growth had been removed, suggested that there may have been some stimulus in the patient which provoked the development of the second growth in the same manner and in the same situation as the first.

In our series of 30 cases, 16 patients were alive and free from symptoms five years after operation; 5 had died of metastatic growths, and so-called local recurrence had taken place in the remaining 9. The present study is based on an examination of the specimens which were removed at operation in these cases, with special reference to the condition of the mucous membrane surrounding the primary growth, in an endeavor to identify any potentially malignant changes. The methods employed were inspection of the gross specimen with the naked eye and with a hand lens and histologic examination of sections made from various parts of the tissue. On inspection we attempted to discover changes in the surface of the epithelium which might be regarded as abnormal. The specimens had all been preserved in solution of formaldehyde, which made definition more difficult than it would have been had the tissue been fresh. With the aid of the hand lens, however, we were able to identify the structures which Dukes has described as adenomas in 10 of the 30 cases. These were sessile outgrowths from the mucous membrane, and they measured from 1 to 4 mm. in diameter. They were situated anywhere up to 15 cm. away from the margin of the growth and sometimes were difficult to discover among the folds of the mucosa. When present, they were usually multiple, although not numerous, the average being three or four per specimen.

16. Michelson: *Zur Multiplicität der primären Carcinome*, Inaug. Dissert., Berlin, E. Streisand, 1889.

17. Thompson, J. W.: *Secondary Resections in Recurring Carcinoma of the Colon*, J. A. M. A. 107:1688-1693 (Nov. 21) 1936.

In 8 cases an irregularity of the surface of the mucosa was observed. This produced an appearance like a "pile carpet" which has been brushed the wrong way. It occurred in diffuse patches, some of which lay close to the growth while others were several centimeters away from it. In the remaining 12 cases we were unable to find any appearance in the mucous membrane which could be regarded as abnormal.

Sections were made and stained with hematoxylin and eosin. Examination of these showed changes both in the subepithelial tissue and in the epithelium itself.

The Subepithelial Tissue.—The significant changes in this tissue appeared to have taken place in the muscularis mucosae and in the lymphoid tissue. Before describing these changes it is necessary for us to enter into a brief consideration of the appearance of these tissues in the normal colon.

The muscularis mucosae is a continuous layer of unstriped muscle which lies immediately subjacent to the bases of the crypts of Lieberkühn. It separates the glandular epithelial elements from the subjacent loose connective tissue, and it is usually covered on its deep surface by a delicate sheath of fibrous tissue. It is perforated by numerous relatively large blood vessels and lymph channels which are between the submucosa and the epithelium (fig. 1 *a*). The function of the muscularis mucosae has been shown by Alvarez¹⁸ to be the adjustment of tension in the superficial epithelial layer by allowing a certain amount of gliding movement on the submucosa and thus preventing any damage to the delicate secreting cells during active peristalsis or the passage of hard scybala. The amount of lymphoid tissue in the subepithelial layer is variable. It occurs as aggregations of lymphocytes situated immediately below the epithelial layer. Beidermann and Trautmann¹⁹ have found that in carnivora these aggregations lie superficial to the muscularis, whereas in herbivora they lie deeper than this layer. Stöhr²⁰ has pointed out that in man they may lie either superficial to or deeper than the muscularis and has drawn attention to their intimate relation to the blood vessels which penetrate this layer. Our own observations lead us to believe that they arise as perivascular infiltrations about these vessels (fig. 1 *b*) and that their ultimate situation depends on the amount of tension in the surrounding tissues, so that they may come to lie either superficial to (fig. 1 *c*) or deeper than (fig. 1 *d*) the muscularis, in whichever position there happens to be space to accommodate them.

18. Alvarez, W. C.: *An Introduction to Gastro-Enterology*, New York, Paul B. Hoeber, Inc., 1940.

19. Biedermann and Trautmann, cited by Siegmund.²⁰

20. Stöhr, P.: Ueber die Entwicklung der Darmlymphknötchen und über die Rückbildung von Darmdrüsen, *Arch. f. mikr. Anat.* 51:1-50, 1898.

Lymphoid aggregations are absent at birth but appear about fourteen days later. They are more numerous in infancy than in adult life, but wide discrepancies are evident in the estimates of the average normal number. Hellman²¹ stated that there are between 7,000 and 21,000 in the colon, but other observers have described single sections of the colon in which they have seen from three or four to two hundred and forty lymphoid aggregations. Obviously the number must be variable, and this can be more readily comprehended when it is realized that the lymphocytes do not reside permanently in the submucosa but that their sojourn there simply represents a transient phase in the life cycle of the cells of the bowel wall. Harrison-Cripps²² expressed the opinion

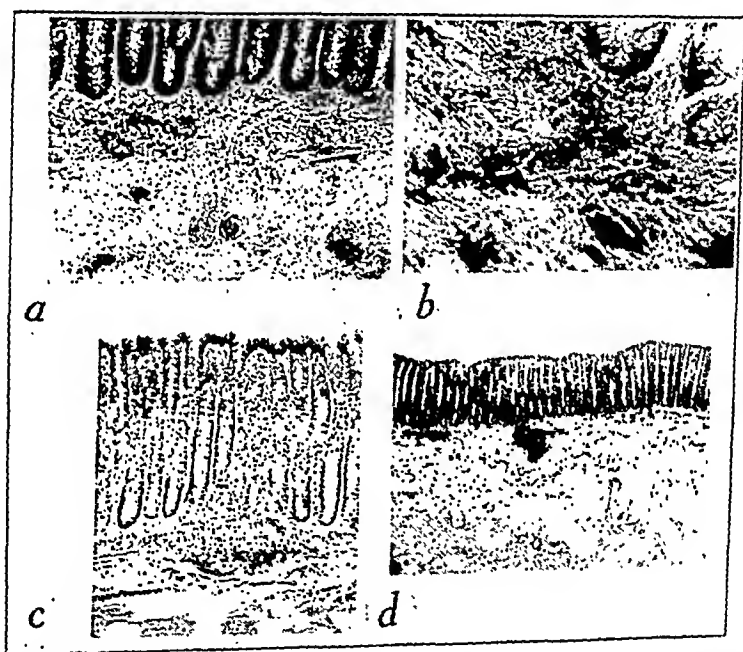


Fig. 1.—Photomicrograph *a* shows blood vessels penetrating the muscularis mucosae ($\times 150$). Photomicrograph *b* shows perivascular infiltration with lymphocytes around a vessel penetrating the muscularis mucosae ($\times 225$). Photomicrograph *c* shows a lymphocytic aggregation lying superficial to the muscularis mucosae, part of which has been broken through; one may note the regular normal appearance of the crypts ($\times 80$). Photomicrograph *d* shows a lymphocytic aggregation deep to the muscularis mucosae; one may note the regularity of the epithelium ($\times 35$).

that the function of lymphocytes in this situation is to replace the epithelial cells and to act as a reserve or basal layer. Modern conceptions of cytology, however, render such a view untenable, and the

21. Hellman, T. S., cited by Siegmund.³⁰

22. Cripps, H.: *Cancer of the Rectum: Its Surgical Treatment*, ed. 5, London, J. & A. Churchill, 1907.

recent experiments of Bunting and Huston²³ have demonstrated that the majority of the lymphocytes from the circulating blood normally terminate their existence by passing into the lumen of the intestine. According to Haden,²⁴ the life span of a lymphocyte is less than twenty-four hours, and this would indicate that any structure composed solely of these cells must be temporary. The size of the individual aggregations is also variable. Hofmeister²⁵ stated that they are larger in well nourished animals than in poorly nourished ones, and Biedermann has demonstrated fluctuations according to the phase of digestion. When a lymphoid aggregation becomes very large it may disrupt the continuity of the muscularis mucosae. Under pathologic conditions it may become encapsulated and acquire a well marked secondary center which shows up as a collection of large pale-staining cells in the center of the lymph follicle. When this stage has been reached, secondary changes become evident in the overlying epithelium. In 100 sections taken at random from apparently healthy colons we observed lymphoid aggregations of sufficient size to disrupt the muscularis mucosae in only 16 cases. In no case was there a formation of encapsulated follicles with secondary centers. In all but 1 of our cases of carcinoma of the colon, however, we found that the muscularis mucosae was disrupted, and it is significant that the one exception occurred in a case in which the carcinoma had arisen in a diverticulum. In 24 of the 30 cases large encapsulated follicles with well formed secondary centers could be demonstrated.

The Epithelium.—Changes were seen in the epithelium only when the follicles were fully developed and contained secondary centers. The primary change was an irregular proliferation of the glandular structures overlying the follicles and the production of atypical glands and cystic formation (fig. 2 a). It would appear that these changes were secondary to and the direct result of the presence of the underlying follicles. The subsequent changes were mainly mechanical in origin. Rupture of a follicle allows the epithelium to prolapse into its substance, which gives rise to the appearance described by Schultze²⁶ and now known as a "Schultze picture." Latta²⁷ has shown that when epithelial cells come

23. Bunting, C. H., and Huston, J.: Fate of the Lymphocyte, *J. Exper. Med.* **33**:593-600 (May) 1921.

24. Haden, R. L.: Principles of Hematology, Philadelphia, Lea & Febiger, 1939.

25. Hofmeister, cited by Siegmund.³⁰

26. Schultze, W.: Ueber Beziehungen der Lieberkühnschen Krypten zu den Lymphknötchen des Dickdarmes, *Zentralbl. f. allg. Path. u. path. Anat.* **16**:99-103 (Jan.) 1905.

27. Latta, J. S.: The Histogenesis of Dense Lymphatic Tissue of the Intestine (*Lepus*): A Contribution to the Knowledge of the Development of Lymphatic Tissue and Blood-Cell Formation, *Am. J. Anat.* **29**:159-200 (July) 1921.

into actual contact with lymphoid tissue there is a tendency to suppression of the more specialized goblet cells and the cells remain in a primitive undifferentiated state. This was evident in our material. The subsequent fate of the prolapsed epithelial cells would appear to be governed by the extent of the lymphatic barrier which surrounds them. When this is considerable their further progress is checked (fig. 2 *b* and *c*), but if it is meager atypical glandular structures composed of primitive epithelial cells may escape into the loose connective tissue of the submucosa (fig. 2 *d*).

Here and there the follicles had ruptured into the lumen of the bowel and caused ulceration. In the process of healing of the ulcers thus

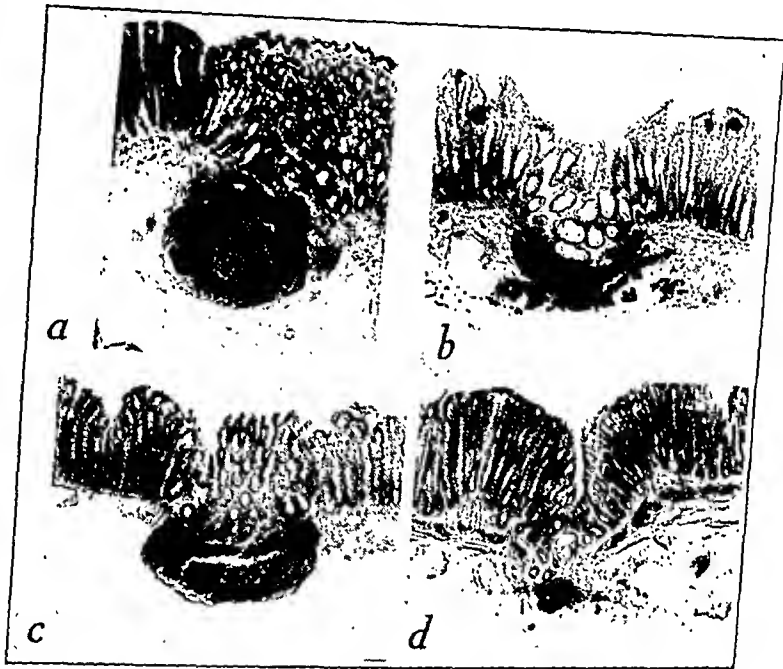


Fig. 2.—In *a* there is a large encapsulated lymph follicle showing a well marked secondary center. One may note the change in the overlying epithelium. In *b*, rupture of a follicle (so-called Schultze picture) is seen, with prolapse of epithelium into lymphoid tissue; one may note the cystic glands overlying the follicle. In *c*, the Schultze picture is observed; one may note the hyperchromatic epithelial cells above and to the left of the follicle. In *d*, there is follicle rupture with epithelial prolapse; one may note the paucity of the lymphoid barrier.

formed epithelial cells had become trapped in the deep layers at the base of the ulcer. These cells also exhibited a more primitive and less differentiated structure than the normal cells (fig. 3 *a*, *b* and *c*). The changes caused by the rupture of follicles were not visible with either the naked eye or the hand lens. In some regions of the intestinal wall, however, the follicles were so numerous that by their influence on the overlying epithelium they had produced a gross irregularity of the

surface which was recognizable as the "pile carpet" appearance previously mentioned (fig. 3 *d*).

Occasionally a small patch of epithelium had become isolated from the rest of this stratum by a circle of large follicles. Progressive enlargement of these follicles had destroyed the muscularis mucosae, and the epithelium had become "pegged down" to the underlying submucosa by the lymph follicles. Contraction of the surrounding muscularis had tended to approximate these fixed points by centripetal compression, and the tissue which they enclosed had consequently become pushed up as a little elevation above the surface of the mucosa (fig. 4 *a*). This was visible with the hand lens and represents the earliest stage in the

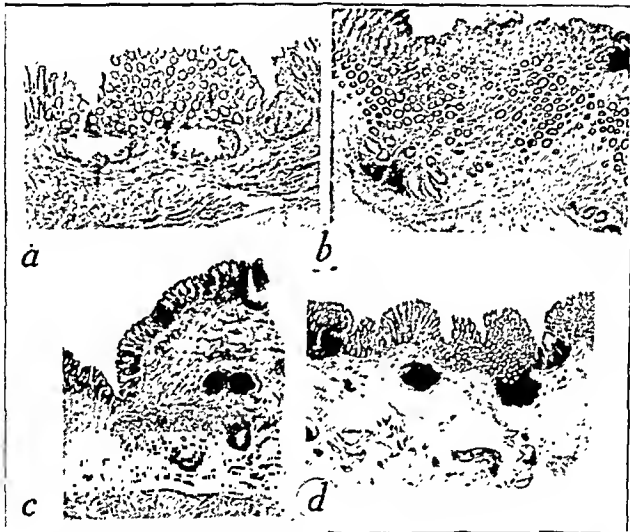


Fig. 3.—In *a* is shown external rupture of a follicle; desquamation and ulceration are about to take place. Photomicrograph *b* shows healed ulceration; one may note epithelial cells trapped in the submucosa. Photomicrograph *c* shows healed ulceration in a case of colitis cystica profunda. In *d* is shown irregular hyperplasia of epithelium overlying lymph follicles; this gives the "pile carpet" appearance on gross examination.

formation of the little structures which Dukes concluded were adenomas. Subsequent stages consisted of irregular hyperplasia of the glandular structures in the isolated portion of the mucosa (fig. 4 *b*), and by the continuation of this process the cells had become more primitive in type, until finally the characteristic appearances of secondary cytoplasmia were evident (fig. 4 *c* and *d*). While changes were taking place in the epithelium, traction, possibly by the passage of fecal material over the surface of the epithelium, had caused the structure to become elongated

and extruded further into the intestinal lumen and thus to form a more or less definite polyp. The lymphoid tissue at the base of this polyp was slowly replaced by fibroblasts, so that ultimately the polyp came to possess a well developed fibrous core.

In summary, then, we have observed changes in the tissues surrounding cancers of the colon. These changes consisted primarily of the enlargement of the lymphoid aggregations in the submucosa with resultant damage to the muscularis mucosae. The subsequent development of large encapsulated follicles with secondary centers produced associated changes in the epithelial cells. By rupture of the follicles some of these cells became displaced into the submucosa. In some cases portions of mucosa became isolated by an encirclement of lymph follicles

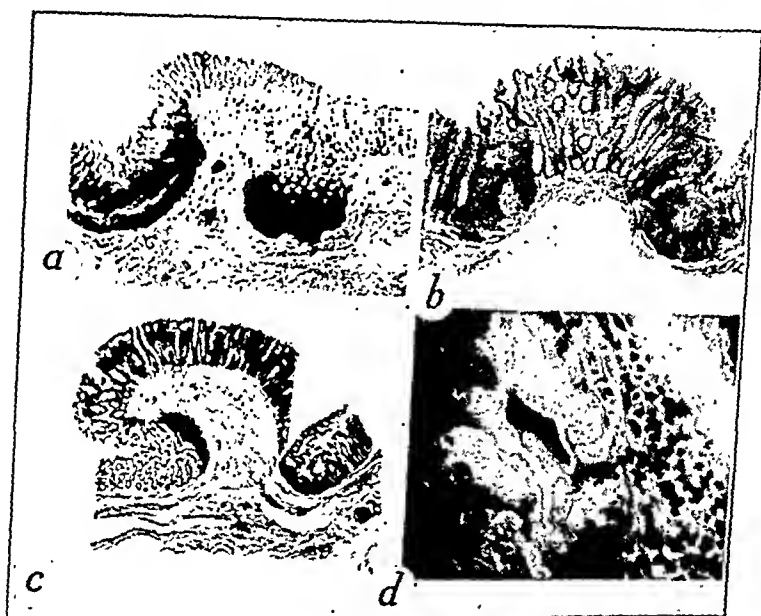


Fig. 4.—In *a*, early polyp formation is present; one may note disruption of the muscularis mucosae by lymph follicles. Intervening epithelium is being extruded into the lumen of the bowel. In *b*, one notes an early polyp with commencing hypoplasia of the glands; in *c*, a later stage of development of the polyp (one may note that the lymphoid tissue at the base is becoming replaced by fibrous tissue), and in *d*, secondary cytoplasmia in the cells of the polyp shown in *c*; one may note large atypical nuclei with large nucleoli.

and became pinched up into the form of polyps. Changes were also noted in the cells of these polyps.

COMMENT

Bland-Sutton,²⁸ in discussing the histologic character of a certain tissue, stated: "It is well to emphasize the point that the microscopical

28. Bland-Sutton, J.: *Surgical Diseases of the Ovaries and Fallopian Tubes, Including Tubal Pregnancy*, Philadelphia, Lea Brothers & Co., 1891.

characters of the mucous membrane do not admit of any difference of opinion. The question is one of interpretation." With the microscope and sections of dead tissue one can see only the structure, and although John Hunter²⁹ has said that structure is the ultimate expression of function the nature of this function can be but a matter for conjecture. This criticism must therefore be applicable to much of what follows.

It is apparent that the tissues in the neighborhood of cancer of the colon differ from those of the healthy colon, and the primary change appears to lie in the development of large lymph follicles in the submucosa around the blood vessels. We have mentioned that these structures are represented in the normal colon, but in a lesser degree. Disruption of the muscularis mucosae is rarely seen in health, and secondary centers have not been observed. We also have cited the view of Bunting and Huston that the majority of the lymphocytes in the circulating blood eventually pass into the lumen of the bowel, presumably to neutralize the toxins of the intestinal contents by the specific action of the lipase which they contain. It is possible that the demand for lymphocytic action may be intermittent and related to the phases of digestion, as is suggested by the work of Biedermann, and that the aggregations of cells in the submucosa may be held to represent a phase of "storage" prior to their discharge into the lumen of the bowel.

Large encapsulated follicles with secondary centers are commonly associated with the recognized inflammatory lesions of the colon. Siegmund³⁰ has drawn particular attention to the presence of large follicles in cases of enteritis nodosa, and Hadfield³¹ recently has shown that the earliest change associated with regional enteritis is the appearance of large lymph follicles containing giant cells. The pathologic process of chronic ulcerative colitis follows a sequence which is similar but more acute. We have demonstrated in the past that in this disease miliary thrombosis of the vessels in the submucosa is followed by miliary abscesses, which in turn form miliary ulcers.

The secondary changes in the overlying epithelium are also found in observed association with the recognized infections. Cystic gland formation has been described in two situations: superficial to the muscularis mucosae in cases of colitis cystica superficialis (Virchow³²)

29. Hunter, J., cited by Garrison, F. H.: *An Introduction to the History of Medicine*, ed. 3, Philadelphia, W. B. Saunders Company, 1921, p. 355.

30. Siegmund, H.: *Die Beteiligung des lymphatischen Gewebe des Darmes an entzündlichen Veränderungen*, in Henke, F., and Lubarsch, O.: *Handbuch der speziellen pathologischen Anatomie und Histologie*, Berlin, Julius Springer, 1929, vol. 6, pp. 311-332.

31. Hadfield, G.: *The Primary Histological Lesion of Regional Ileitis*, *Lancet* 2:773-775 (Oct. 7) 1939.

32. Virchow, cited by Orth.³³

and beneath this layer in cases of colitis cystica profunda (Orth³³). Ulceration is a feature common to regional enteritis and chronic ulcerative colitis, but in both instances it is secondary to changes in the submucosa. The changes which we have observed in our material would therefore appear to resemble those occurring with recognized inflammations of the colon, except that they are milder. That is to say, they represent subclinical inflammatory processes.

We have been able to trace the development of small polypoid growths in the mucosa. The nature of these structures can best be understood by realizing that they belong to the inflammatory group of polyps according to the classification of Wesson and one of us (Bargen)³⁴ and that they are not true adenoma. The adenomatous polyp has been depicted by Schmieden and Westhues³⁵ as arising from a primary epithelial hyperplasia. Polyps of this type, which are commonly seen in cases of familial polyposis, represent a congenital error of development of the epithelium itself and are in no way related to the process we have described. We believe that many misconceptions have arisen through failure to recognize this fact. Dukes expressed the opinion that the small polyps he saw in the mucous membrane surrounding cancers were of the adenomatous type. He observed the presence of the lymph follicles around the necks of the polyps, but he believed that this was a secondary change and represented a "collar catarrh." Graham,³⁶ on the other hand, maintained that all polyps are inflammatory in origin and that they arise as the result of irritation and infection in a susceptible person. Inflammatory change is commonly associated with these tumors, and it is possible for the two types of polyps to coexist in the same bowel. Inflammatory polyps arising in chronic ulcerative colitis by isolation of patches of mucous membrane have been described by Struthers.³⁷ The process which we have described is again similar in nature but milder in degree. Coffey and one of us (Bargen)³⁸ noted the frequent association of large follicles and polyps and expressed the opinion that the follicles were the result

33. Orth, J.: Ueber Colitis cystica und ihre Beziehungen zur Ruhr, *Berl. klin. Wchnschr.* **29**:681-687 (July) 1918.

34. Bargen, J. A., and Wesson, H. R.: Classification of Polyps of the Large Intestine, *Proc. Staff Meet., Mayo Clin.* **9**:789-794 (Dec. 26) 1934.

35. Schmieden, V., and Westhues, H.: Zur Klinik und Pathologie der Dickdarmpolypen und deren klinische und pathologisch-anatomischen Beziehungen zum Dickdarmkarzinom, *Deutsche Ztschr. f. Chir.* **202**:124, 1927.

36. Graham, H. F.: Multiple Adenoma of Colon (Polyposis), *Am. J. Surg.* **5**:234-240 (Sept.) 1928.

37. Struthers, J. E.: Multiple Polyposis of the Intestinal Tract, *Am. J. Surg.* **72**:649-664 (Dec.) 1920.

38. Bargen, J. A., and Coffey, R. J.: Intestinal Polyps: Pathogenesis and Relation to Malignancy, *Surg., Gynec. & Obst.* **69**:136-145 (Aug.) 1939.

of a subclinical inflammation and that they might be intimately connected with the formation of polyps. Our own material convinces us that the changes in the follicles are the primary stage in the formation of polyps and demonstrates clearly that epithelial changes do not take place until the follicles have reached a large size and possess secondary centers. This is in keeping with the sequence of events seen in other diseases, and it seems to be in accordance with the general laws of pathology that the inflammatory reaction should take place in the mesodermal tissue rather than in the epithelial cells. It is hard to see how an epithelial cell which has no phagocytic or other defensive powers could respond to an irritant except by degeneration or disintegration. It must be remembered that any reaction which is commonly seen among the epithelial cells, such as leukoplakia or hyperkeratosis, is essentially degenerative. It seems more probable that the epithelial hyperplasia represents a disordered attempt to repair the damage which has been done to the cells.

Changes in the tissues in the vicinity of cancer have been demonstrated in our specimens. Are these changes "potentially malignant"? Our strongest affirmative argument is that in a considerable proportion of cases cancer did develop in this tissue. This fact and the discovery in the tissue of cells showing definite secondary cytoplasia lead us to believe that we have established the existence in our cases of a potentially malignant region existing prior to and coincidentally with the development of cancer. We believe that this is the result of a subclinical inflammation and is in every way comparable to the potentially malignant region described by the experimenters. The extent of this region we were not able to ascertain, but we observed changes as far as 15 cm. away from the primary neoplasm. We were unable to form any definite opinion as to the nature of the irritant which stimulated the reaction. It is possible that some definite carcinogenic agent may have been present in the contents of the bowel, but it is more likely that the irritant was nonspecific and represented the action of some low grade chemical or of bacteria.

The actual development of malignancy in the potentially malignant region begins in those cells which have become isolated from the remainder of the epithelial layer, either by burial in the submucosa or by segregation as polyps. The factor common to these isolated cells would seem to be their altered environment. MacCarty³⁹ has drawn attention to the importance of local starvation in the causation of migratory hyperplasia, a conception also favored by Warburg,⁴⁰ and it seems probable that this is the factor of prime significance in this

39. MacCarty, W. C.: The Genesis of Cancer, Proc. Staff Meet., Mayo Clin. 12:295-297 (May 12) 1937.

40. Warburg, O.: The Metabolism of Carcinoma Cells, J. Cancer Research 9:148-163 (March) 1925.

instance. The role of the lymphocytes in this respect is doubtful. MacCarty, in papers written with Mahle⁴¹ and Kehrer,⁴² has shown that the local lymphocytic response has a definite relation to the prognosis of cancer, and Murphy and Sturm⁴³ have demonstrated experimentally that lymphoid tissue exerts a resisting influence on the development of malignancy. This would appear to have some bearing on the significance of the Schultze pictures and the lymphoid barrier which we already have mentioned. It may well be that the function of the lymphocytes in the situation is to check the spread of the hyperplasia until the fibroblasts have had time to build a stronger wall for this purpose. If the lymphocytic barrier is small, the epithelial cells can break through



Fig. 5.—Photomicrograph *a* shows carcinoma which has arisen on the basis of a polyp; photomicrograph *b*, carcinoma developing by the amalgamation of several polyps; photomicrograph *c*, carcinoma resulting from rupture of a follicle or from ulceration. Photomicrograph *d* is of the section shown in *c*, viewed under high power objective to demonstrate the abrupt change from normal to cancerous crypts at the point where the muscularis mucosae has been ruptured.

into the loose connective tissue of the submucosa (fig. 2), where there is little to impede the spread of the neoplastic process.

41. MacCarty, W. C., and Mahle, A. E.: Relation of Differentiation and Lymphocytic Infiltration to Postoperative Longevity in Gastric Carcinoma, *J. Lab. & Clin. Med.* 6:473-480 (June) 1921.

42. MacCarty, W. C., and Kehrer, J. K. W.: Possible Defensive Factors in Cancer of the Rectum (a Study of One Hundred and Two Cases), *J. Lab. & Clin. Med.* 7:602-606 (July) 1922.

43. Murphy, J. B., and Sturm, E.: Effect of Stimulation of the Lymphocytes on the Rate of Growth of Spontaneous Tumors in Mice, *J. Exper. Med.* 29:31-34 (Jan.) 1919.

Fitzgibbon and Rankin⁴⁴ were able to trace 22 of 24 cancers directly back to polyps, and Swinton and Warren⁴⁵ were able to demonstrate that 14 per cent of their series of malignant tumors involving the colon had arisen in mucosal polyps. Dukes, too, was able to show from the structure of certain cancers that they had developed from polyps. Some of our own cases (fig. 5*a* and *b*) illustrate this clearly. In other cases, however, there was no evidence of polyps, and we believe that cancer in these cases arose from atypical epithelial cells buried in the submucosa as a result of either ulceration or rupture of the follicle (fig. 5*c* and *d*). This is the type of lesion which Cain and Bensaude described as arising in normal mucous membrane but which we believe develops in a region that has already undergone potentially malignant change. The structure of the small cancer reported by Raven⁴⁶ suggests this mode of origin.

The practical significance of the potentially malignant region is two-fold. In the first place, if one could find some method of recognizing this condition clinically it might be possible to prevent the development of cancer, but as the condition can be recognized only histologically this would seem to be a vain hope. The second point of surgical importance is the fact that the potentially malignant region is larger than the primary growth. If the growth is removed by conservative excision this tissue remains behind, and with it remains the risk of a recurrent lesion, or, rather, of the development of a second primary neoplasm. The problem to be solved is the treatment of the potentially malignant tissue, and time will tell whether this can be done most efficiently by radical surgical removal of the bowel in the neighborhood of the cancer or by widespread irradiation of the tissues after conservative treatment of the primary growth.

SUMMARY

A "potentially malignant" region exists in the colon prior to and coincidentally with the development of cancer, and this region is considerably larger than the part which is occupied by the cancer itself. This region represents the reaction of the tissues to some extraneous influence. As it is an inflammatory reaction, the cells primarily concerned are the mesoblastic cells, which are the natural defensive cells of the body. The effect on the epithelial cells is secondary and represents a stage of partial destruction or impairment of nutrition followed

44. Fitzgibbon, G., and Rankin, F. W.: Polyps of the Large Intestine, Surg., Gynec. & Obst. **52**:1136-1150 (June) 1931.

45. Swinton, N. W., and Warren, S.: Polyps of the Colon and Rectum and Their Relation to Malignancy, J. A. M. A. **113**:1927-1933 (Nov. 25) 1939.

46. Raven, R. W.: Early Carcinoma of the Rectum. Proc. Roy. Soc. Med. **32**:907-908 (June) 1939.

by a stage of attempted repair. Multiple familial polyposis represents a separate entity which is not inflammatory in origin but results from an inborn error of development of the epithelial cells and therefore has an entirely different anatomic structure. The subclinical inflammatory processes resemble in every way the recognized clinical forms of colitis, and the two differ only in degree. The process of repair manifested by the epithelial cells may become disordered (1) if a portion of the epithelium is isolated from the rest of the layer by a ring of lymphoid tissue, as occurs in the formation of polyps, or (2) if epithelial cells become displaced into the deeper part of the submucous tissue, as may happen after rupture of a follicle with or without ulceration. This process of repair in cells removed from their normal situation may give way to malignant anaplasia. Malignant change in the epithelial cells is the result not of chronic irritation or of any specific action of a "carcinogenic agent" but of change of environment of the cells. The potentially malignant region does not represent any specific reaction on the part of the tissues but is simply a region in which an inflammatory reaction has led to a disturbance of the normal environmental relation of some of the epithelial cells.

STUDIES ON PROSTATIC CANCER

II. THE EFFECTS OF CASTRATION ON ADVANCED CARCINOMA OF THE PROSTATE GLAND

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AND

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The thesis of this work may be briefly summarized. In many instances a malignant prostatic tumor is an overgrowth of adult epithelial cells. All known types of adult prostatic epithelium undergo atrophy when androgenic hormones are greatly reduced in amount or inactivated. In this paper evidence is presented that significant improvement often occurs in the clinical condition of patients with far advanced cancer of the prostate after they have been subjected to castration. Conversely, the symptoms are aggravated when androgens are injected. We believe that this work provides a new concept of prostatic carcinoma.

The evidence that prostatic carcinoma is often composed of an adult type of epithelium derives from a study of such tissue with respect to the phosphatase which manifests optimum activity at p_H 5. An important advance in the technic of investigation of the prostate gland was made by Kutscher and Wolbergs,¹ who found that this enzyme is present in large amounts in adult human and monkey prostate glands; indeed, this phosphatase is present in prostate tissue in larger amounts than any phosphatase in any other tissue. Gutman and Gutman² found that the enzyme is present in small amounts in infancy and childhood and is increased during puberty to the high values found in the adult. These

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Dr. Hodges is a Fellow of the Douglas Smith Foundation for Medical Research of the University of Chicago.

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1. Kutscher, W., and Wolbergs, H.: Prostataphosphatase, *Ztschr. f. physiol. Chem.* **236**:237, 1935.

2. Gutman, A. B., and Gutman, E. B.: "Acid" Phosphatase and Functional Activity of the Prostate (Man) and Preputial Glands (Rat), *Proc. Soc. Exper. Biol. & Med.* **39**:529 (Dec.) 1938.

workers³ also found in the prostate of immature monkeys traces of the substance which became markedly increased by injections of androgen but not by administration of estrogen. Gutman, Sproul and Gutman⁴ observed that, in addition to alkaline phosphatase with optimum activity at pH 9, acid phosphatase was markedly increased at the site of osteoplastic metastases of prostate carcinoma. In 1938 Gutman and Gutman⁵ and Barringer and Woodard⁶ found that acid phosphatase in the blood serum of many patients with metastatic lesions from prostatic carcinoma was increased above the value for normal men. Serial, long range study of the acid phosphatase levels in the serum of patients with prostatic cancer was first carried out by Robinson, Gutman and Gutman,⁷ who stated that an upward trend of the curve may signify further metastatic involvement. This method has since been used by others (Woodard and Higinbotham⁸; Huggins and Hodges⁹).

It has long been known that prepuberal castration usually prevents the development of the prostate gland, while castration in adult life causes regression of the accessory sex glands; exceptions are known to have occurred only in rodents. White¹⁰ and Cabot¹¹ reported that castration often brought about clinical improvement in men with benign prostatic hypertrophy, with decrease in the size of the gland; reexamina-

3. Gutman, A. B., and Gutman, E. B.: Adult Phosphatase Levels in Prepubertal Rhesus Prostate Tissue After Testosterone Propionate, *Proc. Soc. Exper. Biol. & Med.* **41**:277 (May) 1939.

4. Gutman, E. B.; Sproul, E. E., and Gutman, A. B.: Significance of Increased Phosphatase Activity of Bone at Site of Osteoplastic Metastases Secondary to Carcinoma of Prostate Gland, *Am. J. Cancer* **28**:485 (Nov.) 1936.

5. Gutman, A. B., and Gutman, E. B.: An "Acid" Phosphatase Occurring in the Serum of Patients with Metastasizing Carcinoma of the Prostate Gland, *J. Clin. Investigation* **17**:473 (July) 1938.

6. Barringer, B. S., and Woodard, H. Q.: Prostatic Carcinoma with Extensive Intraprostatic Calcification, *Tr. Am. A. Genito-Urin. Surgeons* **31**:363 (May) 1938.

7. Robinson, J. N.; Gutman, E. B., and Gutman, A. B.: Clinical Significance of Increased Serum "Acid" Phosphatase in Patients with Bone Metastases Secondary to Prostatic Carcinoma, *J. Urol.* **42**:602 (Oct.) 1939.

8. Woodard, H. Q., and Higinbotham, N. L.: Serum and Tissue Phosphatase Determinations, *J. A. M. A.* **116**:1621 (April 12) 1941.

9. Huggins, C., and Hodges, C. V.: Studies on Prostatic Cancer: I. The Effect of Castration, of Estrogen and of Androgen Injection on Serum Phosphatases in Metastatic Carcinoma of the Prostate, *Cancer Research* **1**:293 (April) 1941.

10. White, J. W.: The Present Position of the Surgery of the Hypertrophied Prostate, *Ann. Surg.* **18**:152 (July) 1893.

11. Cabot, A. T.: The Question of Castration for Enlarged Prostate, *Ann. Surg.* **24**:265 (July) 1896.

tion of this problem¹² confirmed their results and showed that epithelial atrophy was present three months after orchidectomy. In senile dogs with spontaneous cystic enlargement of the prostate, castration or the controlled administration of estrogen¹³ eliminates prostatic secretion and produces prostatic atrophy.

Kahler¹⁴ found no correlation between the number of interstitial cells in the testes and the presence or absence of carcinoma of the prostate gland. In assays of the urine in 3 cases of prostatic cancer an increased output of estrogen and androgen was not demonstrated.¹⁵

Counsellor¹⁶ stated that metastases from carcinoma of the prostate gland subsided after administration of a sterilizing dose of roentgen rays to the testis; he presented no evidence for this statement, however. Young¹⁷ castrated 2 patients with prostatic cancer, with negative results. Huggins and Hodges⁹ made serial observations on the levels of acid phosphatase in the serum of 8 patients in the present series and demonstrated by this objective method that castration and administration of estrogen caused a significant decrease of this enzyme and administration of androgen increased it. The present paper is concerned with an evaluation of the clinical changes induced by such endocrine modifications and with a description of the prostate glands and the testes of patients with prostatic cancer.

METHODS AND MATERIAL

Twenty-one consecutive patients with demonstrable metastases or local extension of prostatic cancer outside the capsule of the prostate were treated by orchidectomy. No patient was refused treatment because of the severity of his illness. The diagnosis was established by standard methods.⁹

Determinations of the levels of acid and alkaline phosphatases in the serum were made by the method of King and Armstrong, as previously described,⁹ and were expressed in the units defined by them. All levels of serum phosphatase in this paper are expressed in units per hundred cubic centimeters of serum. Available

12. Huggins, C., and Stevens, R. E.: The Effect of Castration on Benign Hypertrophy of the Prostate in Man, *J. Urol.* **43**:705 (May) 1940.

13. Huggins, C., and Clark, P. J.: Quantitative Studies on Prostatic Secretion: II. The Effect of Castration and of Estrogen Injections on the Normal and on the Hyperplastic Prostate Gland of Dogs, *J. Exper. Med.* **72**:747 (Dec.) 1940.

14. Kahler, J. E.: Carcinoma of the Prostate Gland, *J. Urol.* **41**:557 (April) 1939.

15. Dingemanse, E., and Laqueur, E.: The Content of Male and Female Hormone in the Urine of Patients with Prostatic Hypertrophy, *J. Urol.* **44**:530 (Oct.) 1940.

16. Counsellor, V. S., in discussion on Herrell, W. E.: Relative Incidence of Oophorectomy in Women With and Without Carcinoma of Breast, *Proc. Staff Meet., Mayo Clin.* **11**:785 (Dec.) 1936.

17. Young, H. H., in Cabot, H.: *Modern Urology*, Philadelphia, Lea & Febiger, 1936, vol. 1, p. 887.

histologic sections of prostate were studied for the presence of acid and alkaline phosphatases by the methods of Gomori.¹⁸

Castration was usually done with the area under local procaine hydrochloride anesthesia. As much of the spermatic cord and serous membranes as possible was left, and drainage was not used. In addition, transurethral resection of the prostate was done in cases 2, 3, 5, 8, 9, 20 and 21, and suprapubic removal of the prostate, which showed benign hypertrophy, was carried out in case 1. Roentgen therapy was not used in any case.

Of the 21 patients, 15 had roentgenologically demonstrable metastases in the pelvis or the spine; most of the patients had both osteoplastic and osteolytic lesions; in case 1 there was a pathologic fracture of the pubis. Three patients (cases 4, 10, 13) had cardiac decompensation. Seven patients were confined to bed because of pain in the bones (cases 4, 5, 6, 10, 13, 14, 17); in case 17 there was involvement of the cauda equina by tumor. Four patients had acute urinary obstruction (cases 1, 2, 8, 21). For 14 patients the erythrocyte counts were between 3,500,000 and 4,500,000, and 2 others had counts of 1,990,000 and 2,000,000.

Serum phosphatase determinations were made before operation only for the last 14 men; 7 had an increase in the levels of both phosphatases above normal, while in case 19 only the alkaline phosphatase was increased.

RESULTS

Acid Phosphatase in the Primary Lesion.—In each of the 8 cases in which sections of the prostate were available for staining for acid phosphatase, the enzyme was present in large amount in the neoplastic epithelium, regardless of whether there was a formation of carcinomatous acini (fig. 1) or of solid sheets of malignant cells. Control examination of the prostate of a newborn infant showed only traces of enzyme, while sections of normal adult and hypertrophic prostates contained amounts comparable with the quantity present in carcinomatous prostatic tissue. From this, we deduce that the prostatic carcinomas examined consisted of a malignant type of adult epithelium rather than of neoplastic cells of a more primitive type.

The Testis.—Data about the testes are given in the table. The weights of the testes, considered singly, varied from 7.8 to 42.8 Gm. In cases 4, 5 and 6 each testis weighed 10 Gm. or less, and there was complete atrophy of the germinal epithelium; the interstitial cells, which were arranged in sheets, were abundant (fig. 2). Unfortunately, it is impossible as yet to express the number of interstitial cells quantitatively. The Leydig cells were identified roughly in normal condition in 15 cases (fig. 3); their number was somewhat reduced in 5 cases and markedly reduced in case 10, that of a patient who was moribund from infectious disease and carcinomatosis before orchidectomy.

18. Gomori, G.: Microtechnical Demonstration of Phosphatase in Tissue Sections, *Proc. Soc. Exper. Biol. & Med.* **42**:23 (Oct.) 1939; *Distribution of Acid Phosphatase in the Tissues Under Normal and Under Pathological Conditions*, *Arch. Path.* **32**:189 (Aug.) 1941.

Levels of Serum Phosphatase.—A detailed description of enzyme activities in these patients has been presented elsewhere.⁹ Briefly, in those patients with marked elevation of serum acid phosphatase, castration caused a prompt and sharp reduction to or toward normal which was maintained for many months. In case 4 there was a high value six months after castration, and in case 16 there was a decrease of only 45



Fig. 1 (case 8).—Acid phosphatase in rich concentration in carcinomatous acini in neoplasm of the prostate. The demonstration of the enzyme in this tissue was made by the method of Gomori.

per cent in seventeen days. The level of alkaline phosphatase of the serum rose after castration and then decreased to or toward the normal range over a period of many weeks. A previously undescribed observation was made in cases 9 and 19, in which the value for serum acid phosphatase was normal; castration was followed by a decided elevation of alkaline phosphatase and was accompanied by a change in the

Levels of Serum Phosphatase and Testicular Data in Twenty-One Cases of Carcinoma of the Prostate

Case	Name	Age, Years	Predominant Nature of Metastases to Bone	Serum Phosphatase, Units per 100 Cc.			Time Since Orchidectomy, Days	Weight of Testes, Gm.		Histologic Nature of Testes *		Postoperative Clinical Status
				Before Orchidectomy		Acid		Basile	Germinal Epithelium	Interstitial Cells		
				Acid	Basile							
1	A. J.	75	Osteolytic	545	5.25	12.75	2	1	Improved	
2	E. K.	64	None	365	2.35	12.75	2	2	Improved	
3	P. G.	74	Osteoplastic	295	3.75	10.5	2	2	Improved	
4	S. R.	72	Osteoplastic	180	90	30	0	2	Died 193 days after operation	
5	G. P.	73	Osteoplastic	70	4.6	31.5	0	2	Unimproved; died 234 days after operation	
6	M. M.	56	Osteoplastic	217	7.5	38	0	2	Improved	
7	J. M.	75	None	118	6	15	0	2	Improved	
8	P. R.	54	Osteoplastic	27.5	22	192	4.5	11	2	2	Improved	
9	J. D.	65	Osteolytic	3	6	103	4.5	25.5	2	2	Improved	
10	C. R.	74	Osteoplastic	75	60	6	44	57	2	2	Improved	
11	E. B.	73	None	1.5	6	143	2.25	8.25	1	0	Died 8 days after operation	
12	L. V.	65	None	1	6	83	5.25	9.75	2	2	Improved	
13	C. B.	61	Osteoplastic	34	78	153	7.5	24	1	1	Improved	
14	J. R.	80	Osteolytic	37	19	146	2.5	15.5	2	2	Improved	
15	O. A.	75	Osteolytic	25	24	44	7.5	20.5	1	1	Improved	
16	P. M.	65	Osteoplastic	52.5	72	17	40	78	1	2	Died 53 days after operation	
17	J. C.	71	Osteoplastic	22	54	34	12.5	39	0†	2	Improved	
18	P. W.	63	Osteoplastic	1.5	9	58	3	12	0†	2	Improved	
19	F. D.	84	Osteolytic	3	15.75	22	4.5	42	2	2	Improved	
20	G. R.	71	None	4.5	9.75	2	1	Improved	
21	G. R.	61	None	3.75	6	22	4.5	11.25	2	2	Improved	
								14	2	2		

* The figures indicate approximately the nature of the cells of the testis: 2, normal; 0, atrophic, and 1, grades intermediate between 0 and 2.
† Hormone injections were given before orchidectomy.

* The figures indicate approximately the nature of the cells of the testis: 2, normal; 0, atrophic, and 1, grades intermediate between 0 and 2.
† Hormone injections were given before orchidectomy.

character of the bony metastases from a rarefying to a condensing type; no significant changes occurred in the levels of acid phosphatase.

Mortality Following Orchidectomy.—Four patients died within a short time after orchidectomy. In case 10, that of a man with auricular fibrillation and cardiac decompensation, death occurred from broncho-

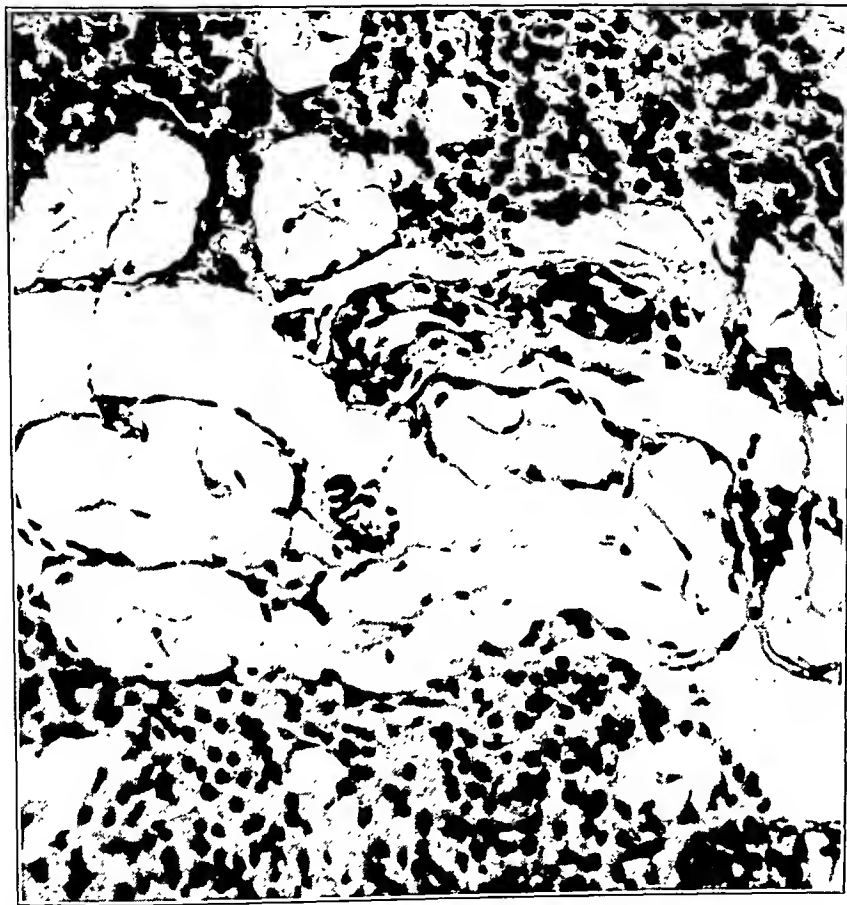


Fig. 2 (case 6).—Complete tubular atrophy of the testis, with solid sheets of interstitial cells, in a case of cancer of the prostate.

pneumonia and acute suppurative arthritis of the knee, eight days after operation. In case 15 death from cerebral apoplexy occurred fifty-three days after orchidectomy. In case 4 cardiac decompensation complicated the convalescence, which was terminated by lobar pneumonia one hundred and ninety-three days after operation. The serum acid phosphatase was 90 units shortly before death; in addition to nodular hyperplasia

of the adrenal cortices, there were several metastatic tumor nodules in the pleura and a diffuse infiltration of carcinoma in the pelvic fascia, producing a thick membrane. The symptoms of cachexia and pain in the bones in case 5 were not greatly relieved, and the patient died two hundred and thirty-four days after operation; this was the most unsatisfactory case in the series.



Fig. 3 (case 13).—Nearly normal testis in a case of carcinoma of the prostate; interstitial cells are shown in the lower left corner.

General Clinical Course After Orchidectomy.—A noticeable improvement occurred in the clinical status of all but 3 patients (cases 4, 5, 10). In addition to the strictly objective changes in serum phosphatase which were usually observed, there was other evidence of improvement.

1. *Changes in Weight:* A gain of 3 to 18 Kg. occurred in all cases within a period of two to eighteen months after orchidectomy (fig. 4). All of the patients who have survived have maintained their gains in

weight. An interesting observation was the development of a large appetite for food, which is particularly unusual for patients with carcinomatous cachexia. McCullagh and Renshaw¹⁹ noticed increased appetite in the castrates whom they studied.

2. Red Blood Cell Count: In general the trend of the erythrocyte count in peripheral blood was upward, although for only 1 patient was a value of 5,000,000 cells per cubic millimeter reached (fig. 4).

3. Neurologic Changes: In 11 cases severe pain was present in the lower part of the back and legs, in the perineum, in the hypochondrium or in more than one of these regions; 7 patients were confined to bed. This symptom improved in all patients within several days after operation, maximum benefit being reached two to eight weeks after castration.

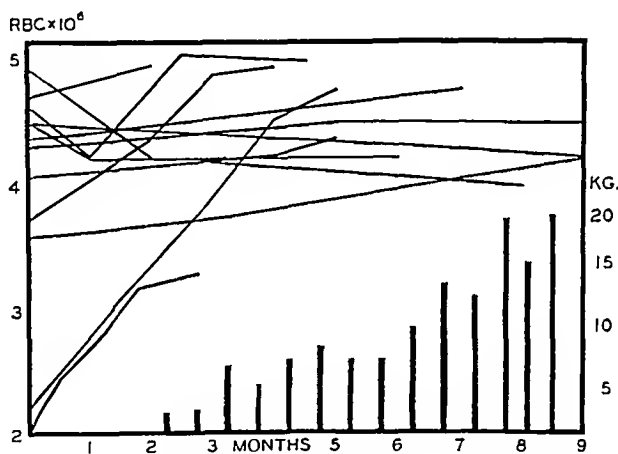


Fig. 4.—Changes in weight and erythrocyte count in peripheral blood following orchidectomy for cancer of the prostate. The red cell counts, in millions per cubic millimeter, are shown as horizontal lines at the top of the figure; the gains in weight are represented by the solid columns arising from the base line.

In 2 cases the relief of pain was only partial, and in 9 it was nearly or quite complete and has been maintained. In all except case 10 the patient became ambulatory.

In case 17 there was evidence of involvement of the cauda equina. The resolution of this lesion is described later in the case reports.

4. Swelling of Lower Extremities: A high grade pitting edema of the ankles and feet developed after orchidectomy in cases 4, 5, 9, 13 to 17 and 20. In case 15 the edema was accompanied by palpable thrombi in the saphenous system; otherwise, the cause of the edema was obscure.

19. McCullagh, E. P., and Renshaw, J. F.: Effects of Castration in Adult Male, *J. A. M. A.* **103**:1140 (Oct. 13) 1934.

The swelling disappeared in each case within four months; in case 4 edema subsequently reappeared, accompanying myocardial decompensation.

5. Sexual Capacity: Sexual desire and penile erections were absent in all cases following castration. No mental changes were observed.

6. Hot Flashes: Such episodes occurred in cases 1 to 3, 6 to 9, 11 and 12, beginning two to six weeks after orchidectomy, and resembled those experienced by women after the menopause. The hot flashes were associated with profuse perspiration and often occurred at night, forcing the patient to throw off the bed covers. The hot flashes were mitigated for many weeks by oral or subcutaneous administration of 1 mg. of stilbestrol daily for five days.

Clinical Changes in the Primary Lesion Following Castration.—Cystoscopic examination of the patients was not carried out with frequency after castration. In case 2 a "permanent" cystostomy opening had been established because of extensive infiltration of the trigon with carcinoma, which was also located around the ureteral orifices; one year after transurethral resection of the neck of the bladder and orchidectomy, the bladder was smooth and without evidence of tumor.

As judged by rectal examination the prostate gland underwent prompt regression in all cases but 1 (case 12), in which the gland had decreased an estimated 50 per cent four months after castration. In all other cases the gland decreased to a small size within twelve weeks after orchidectomy. In the majority of cases the prostate became completely soft and either so small as to be just perceptible or actually impalpable. Usually the seminal vesicles were palpated as small cordlike structures. The decrease in size has been maintained throughout the periods of observation, the longest of which has been eighteen months.

Changes in Roentgenograms of Bony Metastases After Orchidectomy.—It is difficult to compare serial roentgenograms of the pelvis because of differences in position of the patient and in the technic of filming from time to time. In our opinion, certain unequivocal changes were observed associated with increases in the density of bone after castration. In all cases in which metastases were present which were followed for long periods (cases 1, 3, 4, 5 to 9, 13, 14), increased osteosclerosis of the metastases was observed within three to six months after castration. In case 9 such increased calcification allowed recognition of minute osteolytic lesions which had previously been overlooked. Unfortunately, it is impossible to tell whether increased sclerosis signifies an advance in the neoplastic process or is a sign of healing, with formation of bone as a repair mechanism. In some cases this preliminary sclerosis was not followed by an increase in the size of the lesions in six months, and there was evidence of healing in the roentgenograms. A pathologic fracture which was present in case 1 (fig. 5 A) became united, and this

was followed by a distinct regression (fig. 5 *B*) in the metastatic lesions in the pelvis during eighteen months.²⁰

Effect of Injections of Androgen.—Intramuscular injection of 25 mg. of testosterone propionate²¹ daily for eleven to eighteen days in 3 cases

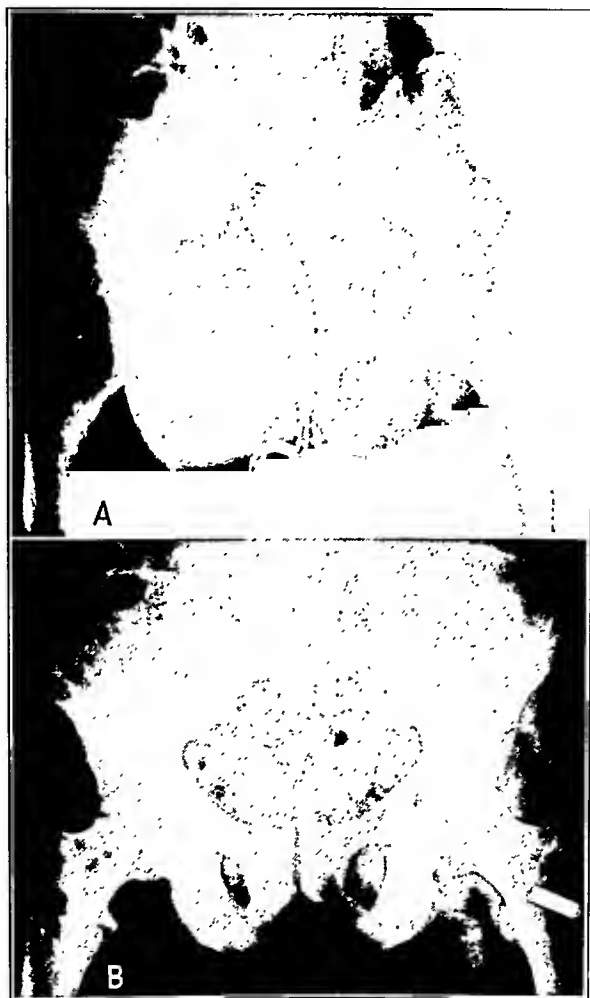


Fig. 5 (case 1).—Roentgenograms of the pelvis. *A* shows diffuse osteoplastic and osteolytic metastases from carcinoma of the prostate. Note the fuzziness of the right ischium and pubis and the pathologic fracture in the latter. *B* was taken eighteen months after bilateral orchidectomy. As compared with *A*, the right ischium and pubis are now sharp and clear and the pathologic fracture has healed.

20. A preliminary report of this case has been published: Huggins and Stevens¹² [case 2].

21. Dr. Erwin Schwenk, of Schering Corporation, supplied this material.

in which bony metastases were present caused an increase in the acid phosphatase of the serum. The patients complained of an increase of pain in the legs after injections had been given for one week.

REPORT OF CASES

CASE 1.—A. J., a white man 75 years of age, had acute retention of urine, and a diagnosis of associated benign hypertrophy and cancer of the prostate was made.³⁰ His weight was 50 Kg. The chief clinical features were in the pelvis. The prostate gland was greatly enlarged (4+); on the right side it was soft to palpation, but on the left there was extensive stony induration extending along the left seminal vesicle. Roentgenograms showed extensive osteolytic metastases to both sides of the pelvis, with a pathologic fracture of the right pubis (fig. 5A). On Oct. 16, 1939 orchidectomy was done, and on Jan. 10, 1940 the prostatic adenoma was enucleated. On March 20, 1940 his weight was 57 Kg., the prostatic bed was soft and no signs of carcinoma could be detected. On March 20, 1941 his weight was 64 Kg., and the results of rectal examination were the same as one year previously. The patient was ambulatory and had no symptoms. Roentgenograms of the pelvis showed healing of the fracture and a regression of the neoplastic process (fig. 5B).

CASE 14.—J. R., a white man 80 years of age, complained of pain in the dorsal and lumbar regions of the back for five months preceding his admission to the hospital on Oct. 30, 1940. For two months he had spent most of his time in bed and was unable to walk without intense pain and fatigue. There had been a loss of 17 Kg. in weight in three months. On examination it was found that the patient could not change his position from lying to sitting in bed without agony accompanied by distention of the veins of his neck. The prostate was slightly enlarged (2+) and there was a hard nodule (1 cm. in diameter) in the apex of the gland about the membranous urethra. Roentgenograms showed diffuse osteolytic lesions in the pelvis with partial collapse of the body of the sixth dorsal and the second lumbar vertebra. The levels of serum phosphatase were: acid, 37 units; alkaline, 19 units. His weight was 62 Kg. The only treatment was orchidectomy, performed on Nov. 12, 1940. Within five days thereafter he was able to raise himself promptly from the lying to the sitting posture. On November 26 the prostate gland was soft and just palpable. On April 21, 1941 the patient considered himself well; he had little pain in the lumbar region, and he had just spaded a garden 40 by 50 feet (12.2 by 15.2 meters) without trouble; his weight was 74 Kg. The levels of serum phosphatase were: acid, 2.25 units; alkaline, 13.5 units.

CASE 17.—J. C., a 71 year old white man, was apparently well until six months before admission, when pain in the lower part of the abdomen and of the back developed acutely. These pains persisted and were so severe that much sedation, including opiates, was given. Three weeks before admission numbness developed over the buttocks and the posterior aspect of the thighs, accompanied by urinary retention and complete fecal incontinence. There was a progressive loss of 14 Kg. in weight. On examination the patient was cachectic; he weighed 46 Kg. There was atrophy of the buttocks and of all of the muscles of the legs, especially of the hamstring group. The knee and ankle tendon reflexes were absent. The Naffziger test was positive. A sensory map showed a saddle area of anesthesia involving the skin dermatomes supplied by the second to the fifth sacral segment inclusive; a

decubitus ulcer was present over the sacrum. The anal sphincter was atonic, and there was a continuous involuntary passage of feces. Lumbar puncture yielded xanthochromic fluid with an increased protein content in which a coagulum formed spontaneously on standing. The prostate was slightly enlarged (2+), stony hard and nodular, with much induration along the right seminal vesicle and the base of the bladder. Roentgenograms showed extensive osteoplastic metastases to all bones of the pelvis, the lumbosacral portion of the spine and the upper parts of the femurs. The suffering of the patient seemed acute.

The only treatment was bilateral orchidectomy, performed on March 5, 1941. Within three days the pains had nearly completely disappeared. On the fifth post-operative day he was able to urinate with slight incontinence; sedatives were no longer required. On April 8 the patient was free from pain and was ambulatory; slight fecal incontinence was occasionally manifested. On April 28 he had a good appetite and had gained 11 Kg. in weight; the prostate gland was small and all induration had disappeared; fecal incontinence had disappeared, and the sphincter tonus was good, although not quite normal. The decubitus ulcer over the sacrum had nearly healed. Strength in the muscles of the legs was fairly good. The heel to knee test was well done. The knee jerks were normal; the ankle reflexes were absent. The Naffziger test was negative. There was a contraction in size of the saddle area of sensory disturbance; hypalgesia and hypesthesia were present in this area, but there was no actual anesthesia. Clear normal fluid was obtained by lumbar puncture.

COMMENT

It is difficult to evaluate subjective evidence elicited from patients with advanced cancer while under treatment; even changes in weight and in hemoglobin level may reflect the influence of many psychic factors. As has previously been stated, serial determinations of the levels of serum phosphatase provide an objective method of following the course of the disease. We have previously demonstrated in the present group of patients that the elevated levels of phosphatase usually returned to or toward the normal values when androgens were decreased or inactivated. It seems clear from less objective standpoints also that castration effects a significant benefit in the clinical condition of many patients with advanced cancer of the prostate, while in others improvement is less marked.

The basis for improvement is simple when it is realized that the location and amount of acid phosphatase characterize carcinoma of the prostate as being often (if not always) composed of adult epithelium; adult epithelium of the prostate undergoes regressive changes when the production of androgens is eliminated. Clinical studies of patients with several types of tumors of the adrenal cortex and observations on rodents have demonstrated that androgens are formed in varying amounts in extragonadal sources, especially in the adrenal²²; thus, cas-

22. Burrill, M. W., and Greene, R. R.: Androgenic Function of the Adrenals in the Immature Male Castrate Rat, *Proc. Soc. Exper. Biol. & Med.* **40**:327 (March) 1939.

tration in the guinea pig is not accompanied by complete regression of the accessory sex glands,²³ and prepuberal castration of the rat does not greatly interfere with the puberal development of the prostate²⁴ until the animal is 35 or more days of age. In the cases in this series in which the results of orchidectomy were unsatisfactory, was enough androgen produced in extragonadal loci to activate the carcinoma? This question cannot be answered at the present time.

Hormonal influences on cancer have attracted attention for many years. It is inappropriate to give a complete review of their effect at this time. Beatson²⁵ introduced ovariectomy as a treatment of advanced cancer of the breast, and beneficial results have been reported in certain cases by many workers.²⁶ Lathrop and Loeb²⁷ showed that ovariectomy in young mice reduced the incidence of mammary tumors in strains in which the spontaneous incidence of this disease was high. Murphy and Sturm²⁸ observed that gonadectomy increased the resistance of immature male and female mice to implantation and growth of transplantable tumor.

In his review of 1,000 cases of prostatic cancer Bumpus²⁹ found that two thirds of the patients in whom metastasis had occurred at the time of examination died within nine months. There is a great variability in the length of life of patients with prostatic cancer, and some live more than ten years after discovery of the tumor. It is obvious that insufficient time has elapsed to tell whether complete regression of the tumor has

23. Sayles, E. D.: Postnatal Development of Reproductive System in Male Guinea Pigs and Its Relation to Testis Hormone Secretion, *Physiol. Zool.* **12**: 256 (July) 1939.

24. Price, D.: Normal Development of the Prostate and Seminal Vesicles of the Rat, with a Study of Experimental Post-Natal Modifications, *Am. J. Anat.* **60**: 80 (Nov.) 1936.

25. Beatson, G. W.: On the Treatment of Inoperable Cases of Carcinoma of the Mammar, *Lancet* **2**:104, 1896.

26. Lett, H.: An Analysis of Ninety-Nine Cases of Inoperable Carcinoma of the Breast Treated by Oophorectomy, *Lancet* **1**:227, 1905. Daland, E. M.: Analysis of Cases at Pondville Hospital: Cancer of Breast, *Am. J. Cancer (supp.)* **15**:2361 (July) 1931. Ahlborn, H.: Castration by Roentgen Rays as an Auxiliary Treatment in the Radiotherapy of Cancer Mammar, *Acta radiol.* **11**:614, 1930. Taylor, G. W.: Evaluation of Ovarian Sterilization for Breast Cancer, *Surg., Gynec. & Obst.* **68**:452 (Feb.) 1939.

27. Lathrop, A. E. C., and Loeb, L.: Further Investigations on the Origin of Tumors in Mice, *J. Cancer Research* **1**:1 (Jan.) 1916. Loeb, L.: The Significance of Hormones in the Origin of Cancer, *J. Nat. Cancer Inst.* **1**:169 (Oct.) 1940.

28. Murphy, J. B., and Sturm, E.: Effect of Prepuberty Castration on Subsequent Cancer Implantation, *J. Exper. Med.* **42**:155 (Aug.) 1925.

29. Bumpus, H. C.: Carcinoma of Prostate: Clinical Study of One Thousand Cases, *Surg., Gynec. & Obst.* **43**:150 (Aug.) 1926.

followed orchidectomy in any case in this series, but it can be stated that the clinical and serologic improvement following castration has been considerable in some cases.

SUMMARY AND CONCLUSIONS

In each of 8 cases in which tissue from the primary prostatic cancer was examined for acid phosphatase the high content and distribution of this enzyme in the cells resembled those in normal adult prostatic epithelium; in many cases, at least, prostatic cancer is an overgrowth of prostatic cells of an adult type.

In 21 cases castration was carried out for far advanced or metastatic carcinoma of the prostate; 4 patients died within eight months after the operation; in 2 cases the operation was done too recently to allow deductions as to its efficacy, and in 15 cases appreciable clinical improvement occurred. The objective evidence of benefit after orchidectomy consisted of a great decrease in the levels of serum phosphatase in all but 2 cases, an increase in weight (and appetite), an increase in the red cells of the peripheral blood, a decrease in the amount of pain, shrinkage of the primary lesion, increased density of the metastatic lesions in the roentgenograms and in 1 case improvement in neurologic signs of compression of the cauda equina by metastases. The improvement was greater than we have observed in any case in which far advanced or metastatic cancer was treated in any other way. It is certain that in many cases regression of the neoplasm is not complete.

Untoward effects of castration were temporary swelling of the ankles, development of hot flashes and abolition of sexual capacity. The hot flashes were eliminated by administering estrogen.

Injectons of androgen caused an increase of pain.

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RECURRENCE OF HYPERTHYROIDISM

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Persistent or continuing hyperthyroidism is a condition in which after subtotal thyroidectomy the disease again becomes evident, either immediately or in a relatively short time. With recurrent hyperthyroidism, on the other hand, there is complete relief from the disease for a considerable period before it again becomes manifest. The dividing line between these two types of hyperthyroidism after operation is somewhat arbitrary. Thompson, Morris and Thompson¹ said that the condition is recurrent if there is a return to normal for even one month after operation. Bisgard² sets this dividing line at eight weeks; Jackson,³ at three months; Clute and Veal,⁴ at six months, and Young,⁵ at one year. I believe that a year is a likely period, since a patient who shows a return of symptoms with an elevated basal metabolic rate in nine months or so probably has a continuation rather than a recurrence of the disease. The probability that the disease was actually cured in the interim is small. In view of the arbitrariness of this figure, in the present series of cases one year has been used as the dividing line between persistence and recurrence.

REASONS FOR RECURRENCE AND PERSISTENCE

The primary reason for the occurrence of hyperthyroidism after operation is that subtotal thyroidectomy is an attack on merely a manifestation of the disease in the thyroid gland. It is, in fact, surprising that recurrence is not more frequent, since patients with

From the Thyroid Clinic and the Surgical Service, St. Luke's Hospital.

Presented before the Surgical Section of the New York Academy of Medicine, April 5, 1940.

1. Thompson, W. O.; Morris, A. E., and Thompson, P. K.: Thyrotoxicosis Following Subtotal Thyroidectomy for Exophthalmic Goiter, *Arch. Int. Med.* **46**: 946-978 (Dec.) 1930.

2. Bisgard, J. D.: Persistent Hyperthyroidism: Case Reports, *Nebraska M. J.* **20**:46-50, 1936.

3. Jackson, A. S.: The Prevention of Persistent and Recurrent Hyperthyroidism, *Surg., Gynec. & Obst.* **58**:590-594, 1934.

4. Clute, H. M., and Veal, J. R.: End-Results of Surgery in Exophthalmic Goiter, *J. A. M. A.* **99**:642-647 (Aug. 20) 1932.

5. Young, T. O.: Recurrent and Continuing Hyperthyroidism, *Am. J. Surg.* **39**:104-111, 1938.

hyperthyroidism have an inferior basic nervous equipment with which to meet the strains of everyday life, and except for what rehabilitation can be done after operation, the cause cannot be removed. A number of writers on this subject⁶ have expressed doubt of the permanence of cure and have concluded that in most cases there is lasting damage to the nervous system which insures recurrence of the disease in the presence of the proper stimuli. A number of late recurrences have been reported. Pemberton⁷ observed one twenty-one years after operation, but this is unusual. The latest one in this series was at six and one-fourth years, with the majority occurring between three months and one and one-half years after operation.

A number of specific reasons for persistence and recurrence are known. In cases of immediate continuation of symptoms, in most cases of symptoms recurring within one year and in rare cases of later true recurrence the probable cause is the removal of too little thyroid tissue at operation. Too large remnants of the lateral lobes may have been left; the isthmus may not have been touched; a pyramidal lobe may have been left, or an intrathoracic portion of a nodular goiter may have been overlooked.

In the great majority of cases recurrence and persistence occur with the diffuse or hyperplastic type of toxic goiter. With the nodular toxic goiter they are unusual. Statistics on the proportion of each depend to a great degree on the accuracy of the surgical and pathologic diagnosis. Microscopic distinction is not always reliable, and many hyperplastic thyroids which have undergone marked iodine involution preoperatively are called adenomatous or colloid goiters. With accurate distinction between these two types of hyperthyroidism, however, it can be said that the diffuse type is about ten times as likely to recur as is the nodular.

Lahey, Cattell and Perkin⁸ have shown that the duration of the hyperthyroidism before operation is of importance in the incidence of

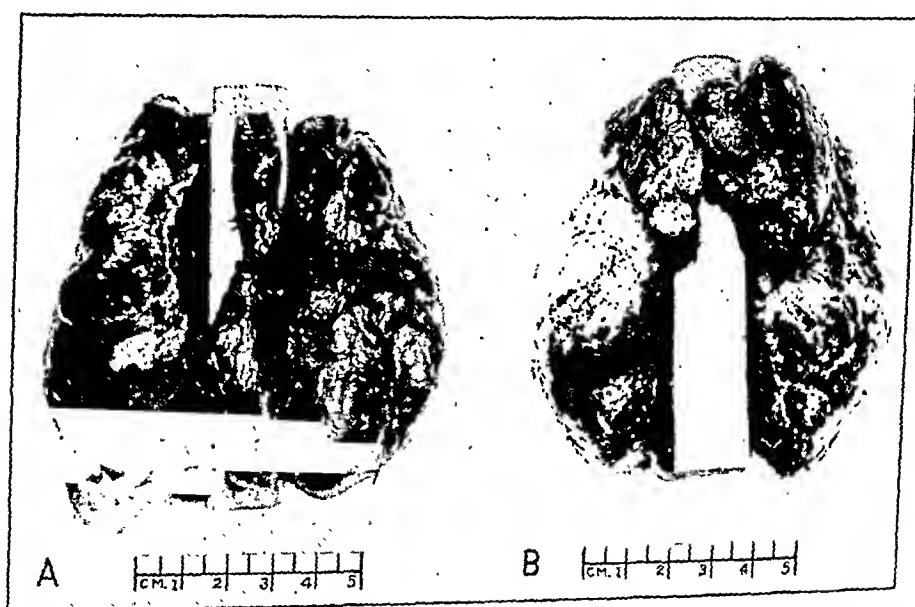
6. McQuillan, A. S., and Breidenbach, L.: Morbidity Following Goiter Operations, *Ann. Surg.* **106**:169-182, 1937. Else, J. E.: Present Status of Our Knowledge of Recurrent Goiter, *West. J. Surg.* **38**:595-604, 1930. Fulton, N. M.; Schnitker, M. A., and Cutler, E. C.: Recurrent and Persistent Thyrotoxicosis Following Thyroidectomy, *ibid.* **46**:619-627, 1938. Haines, S. F., and Pemberton, J. deJ.: Recurrent and Persistent Hyperthyrotoxicosis, *Arch. Int. Med.* **57**:1104-1114 (June) 1936.

7. Pemberton, J. deJ.: Recurring Exophthalmic Goiter: Its Relation to the Amount of Tissue Preserved in Operation on the Thyroid Gland, *J. A. M. A.* **94**:1483-1489 (May 10) 1930.

8. Perkin, H. J., and Cattell, R. B.: Blood Iodine Levels Related to Recurrence of Hyperthyroidism, *Surg., Gynec. & Obst.* **68**:744-748, 1939. Perkin, H. J.; Lahey, F. H., and Cattell, R. B.: Blood Iodine Studies in Relation to Thyroid Disease, *New England J. Med.* **214**:45-52, 1936.

recurrence. In their studies on blood iodine they found that in cases in which the duration of symptoms was nine months or less there were usually an elevated preoperative value for blood iodine and a low post-operative recurrence rate. On the other hand, in cases in which the duration of symptoms was over one year there were usually a normal value for blood iodine and a high recurrence rate. Recent studies on blood iodine (Hinton, Eckerson and Bruger⁹) in a somewhat smaller series of cases have not, however, entirely borne this out.

Social or economic problems, nervous shocks, endocrine adjustments and foci of infection can all be factors in inciting recurrent hyperthyroidism. These are a few of the immediate causes mentioned:



Anterior (A) and posterior (B) view of a large hyperplastic thyroid removed at operation. The wooden cylinder denotes the position of the trachea. This illustrates some of the problems of subtotal thyroidectomy. There are high, retro-tracheal superior poles extending almost completely around the trachea posteriorly, a fair-sized pyramidal lobe and a large isthmus. If any of these were not removed, considerable thyroid tissue would be left and the likelihood of persistence greatly increased.

going back to work too soon; loss of husband's job; financial worries; care of a large family; unhappiness at home; death of a friend; suicide of a relative; pregnancy; menopause; extraction of teeth, and acting as donor for a blood transfusion.

9. Hinton, J. W.; Eckerson, E. B., and Bruger, M.: Iodine Metabolism in Thyroid Disease, *Ann. Surg.*, to be published.

INCIDENCE OF PERSISTENCE AND RECURRENCE

As Thompson, Morris and Thompson¹ stated, the incidence of recurrent hyperthyroidism in the cases reported in the literature varies from 0.25 to 25 per cent. In their series it was 19.5 per cent. Clute and Veal⁴ in 1932 reported an incidence of 12.3 per cent in completely followed cases, and Cattell¹⁰ in 1939 reported 3.3 per cent of reoperations. Pemberton⁷ and Haines and Pemberton,¹¹ in reporting a 2.9 per cent rate, said that, counting the probable recurrences in patients who did not return for follow-up, the incidence at the Mayo Clinic was "certainly not more than 5 per cent."

This paper is a study of 469 patients with toxic thyroids operated on and seen preoperatively and postoperatively in the thyroid disease clinic at St. Luke's Hospital in the ten year period from 1930 to 1939 inclusive and a study of the 34 recurrences which occurred among these patients. Two of the 34 patients in whom recurrence took place had had previous thyroidectomies elsewhere before coming to St. Luke's.

During the five year period from 1930 to 1934 inclusive (this period has been used for more intensive study because of the longer follow-up), 224 patients were operated on, 176 with the diffuse hyperplastic type of goiter and 48 with the nodular type. In this group there occurred 8 persistences and 13 recurrences, a total of 21, and all occurred with the diffuse type of goiter, none with the nodular type. This makes a total recurrence rate of 9.3 per cent. Among these 224 patients there were 5 operative deaths, and 202, or 90.1 per cent, were followed for one to six years. Two of these patients died of other causes within one to two years but were followed until the time of their death.

Unless a patient with this disease is seen at regular intervals for a period of years after operation the presence or absence of recurrence cannot be known. This is especially true of mild transient recurrence. Follow-up by letter and reexamination after a lapse of years cannot give accurate statistics. One hundred and fourteen of the 224 patients operated on in this five year period (50.8 per cent) have been followed in the thyroid disease clinic continuously and completely up to the time of writing. This gives a five to ten year follow-up, during which the clinic was never out of touch with any of these patients. This is a unique series of cases.

Of the 21 patients with recurrent or persistent hyperthyroidism mentioned previously as having been operated on in this period, 16 have

10. Cattell, R. B., and Perkin, H. J.: Recurrent Hyperthyroidism: Likelihood of Recurrence in Relation to Blood Iodine Level, *West. J. Surg.* **47**:55-61, 1939.

11. Haines, S. F., and Pemberton, J. deJ.: The Control of Hyperthyroidism Following Partial Thyroidectomy by Removal of Unusually Small Amounts of Thyroid Tissue, *Proc. Staff Meet., Mayo Clin.* **9**:769-771, 1934.

been continually followed to the time of writing and 1 until his death. The 4 remaining patients were lost to follow-up within three years after their second attack of hyperthyroidism. Since, however, these 4 and the 1 who died were carefully observed until recurrence took place and for varying periods thereafter, the total of 21 has been reached for the 114 completely and continuously followed patients. This makes an incidence of 18.4 per cent. Although this figure is slightly high, it must be realized that patients who have symptoms are more likely to return to the clinic than are those who are well.

TREATMENT OF RECURRENT HYPERTHYROIDISM AND THERAPEUTIC RESULTS

The treatment of persistent and recurrent hyperthyroidism is, with certain exceptions, similar to the treatment of the primary disease—the use of iodine, roentgen therapy and surgical intervention, or a combina-

TABLE 1.—*Summary of Operative Cases in the Five Year Period from 1930 to 1934 Inclusive*

	Cases Followed		Recur- rences	Recurrence Rate, Percentage
	Number	Percentage		
Total.....	224	21	9.3
Followed 1 to 6 years.....	202	90.1	21	10.4
Followed continually and completely for 5 to 10 years.....	114	50.8	21	18.4

tion of these. For mild recurrent hyperthyroidism or for the persistent condition in many cases, especially when there is no clinical regeneration of the remnants, compound solution of iodine U. S. P. alone at the rate of 5 to 10 minims (0.3 to 0.6 cc.) three times a day is effective. It may not cure the disease but it entirely relieves the symptoms, and it can be administered for years without ill effect. One patient has been treated for a mild recurrence with iodine alone for over six and one-half years, and, although she has appeared quite well for one and one-half years, she still has some symptoms on discontinuing the medication and resumes it occasionally.

Roentgen therapy alone or in combination with compound solution of iodine U. S. P. is more effective for the recurrent than for the primary type of this disease, especially when there is little or no regeneration of the remnants. Cures have been obtained in 55.5 per cent of the cases.

Reoperation is, of course, the most dramatic treatment and the one giving the highest percentage of cures, but it carries a rather high proportion of complications. In 7 secondary operations 3 complications occurred. These were unilateral paralysis of the recurrent nerve in 2

cases, in 1 of which it was temporary, and postoperative hemorrhage in 1. Definite persistence of the hyperthyroidism in 1 case was noted.

Reoperation has been reserved for patients with considerable regeneration, severely toxic patients and patients who did not respond to conservative measures. Haines and Pemberton¹¹ reported 3 cases of recurrent hyperthyroidism in which the patients were not helped by conservative means but were cured by removal of 1 Gm. or less of thyroid tissue.

Of the series of 21 patients with the recurrent or persistent condition, 5 were treated with compound solution of iodine U. S. P. alone, and 1 was cured. Nine were given roentgen therapy or iodine and roentgen therapy, and 5 were cured. Seven had reoperation alone or in conjunction with iodine and roentgen therapy, and 6 were cured. On 1 of these an incomplete secondary operation was done because of hemorrhage, and roentgen therapy was given immediately after the operation.

TABLE 2.—*Treatment of Recurrent Hyperthyroidism and Results*

Type of Treatment	Cases	Cures	Percentage of Cures
Iodine alone	5	1	20
Roentgen therapy, or iodine and roentgen therapy....	9	5	55.5
Reoperation, with or without iodine and roentgen therapy	7	6	85.7
Total.....	21	12	57.1

In another an area of carcinoma was found at the second operation; this patient received roentgen therapy for the carcinoma and compound solution of iodine U. S. P. because of a mild persistence of hyperthyroidism.

Thus, of these 21 patients, 12, or 57.1 per cent, were cured, 54.6 per cent with recurrent and 62.5 per cent with persistent hyperthyroidism. Eight still have hyperthyroidism but are not incapacitated by it, and 1 died of the recurrent disease. He had had three previous subtotal thyroidectomies within eight months before coming to St. Luke's. A subtotal excision of the remnants was done in 1930, and after this he was well for five years. He then had a recurrence and was kept comfortable with iodine for about three years. He was admitted to St. Luke's in coma eight years and two months after his operation and died in thyroid crisis. Autopsy showed small hyperplastic thyroid remnants.

PERCENTAGE OF CURES OF HYPERTHYROIDISM

Of 114 completely and continually followed patients operated on at St. Luke's Hospital in the five year period from 1930 to 1934 inclusive, 93, or 81.5 per cent, were cured of their hyperthyroidism by the original

operation. Twelve of the 21 patients with persistent or recurrent hyperthyroidism, or 57.1 per cent, were cured. At the time of writing 105 of the 114 patients, or 92.1 per cent, are cured.

SUMMARY AND CONCLUSIONS

A number of reasons for the persistence and recurrence of hyperthyroidism after operation are suggested. The true cause will not be revealed until the cause of hyperthyroidism is definitely known.

The size of the remnant of the thyroid left at the primary operation should vary with the individual patient. Suggestions are made to obviate the leaving of too much thyroid tissue. Generally smaller remnants should be left.

Statistics on recurrence rates should be based on patients who are continually and completely followed.

After operation, a patient with a toxic thyroid should be seen every three months for a year, every six months for two more years and every year for as long as it is possible to keep in touch with him. This will allow any recurrence to be noted and treated early.

The treatment of persistent and recurrent hyperthyroidism depends on the individual case and on the severity of the disease. It consists of administration of iodine, roentgen therapy and surgical intervention or a combination of these. Rehabilitation of the patient should also be attempted by the social service department.

Miss Madeline Hall, of the social service department, made possible the careful follow-up studies on which this paper is based.

THE CEPHALIN-CHOLESTEROL FLOCCULATION TEST IN CASES OF DISEASE OF THE LIVER

WITH SPECIAL REFERENCE TO THE DIAGNOSIS OF MILD
AND UNSUSPECTED FORMS

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Increasing knowledge of the physiology of the liver has established the vital importance of the integrity of this organ for normal body activity and economy. Moreover, it has awakened a keener appreciation of the potential effects of disturbed hepatic function, especially as it relates to disorders of digestion and metabolism. Nevertheless, the clinical recognition of disease of the liver has attained a relatively high degree of accuracy only with regard to the advanced or the terminal stages of such disease. The early and mild forms frequently remain undiagnosed and are accorded little if any consideration. Present day tests of liver function are, with rare exceptions,¹ of limited diagnostic value in cases of early or mild involvement, owing to the remarkable regenerative capacity and functional reserve with which the liver is endowed.

Recently Hanger² observed that the serums of patients with disease of the liver are capable of flocculating a cephalin-cholesterol emulsion, while, in contrast, normal human serums produce no flocculation. He regarded this reaction as an index of active disease of the liver parenchyma and proposed it as a means of differentiating obstructive from

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From the Department of Medicine and the Department of Metabolism and Endocrinology, Michael Reese Hospital, and the Department of Medicine, Northwestern University Medical School.

1. Rosenberg, D. H., and Soskin, S.: The Azorubin S Test of Liver Function: An Evaluation with a Comparative Study of the Bromsulphalein and Hippuric Acid Tests, *Ann. Int. Med.* **13**:1644 (March) 1940. Soffer, L. J., and Paulson, M.: Comparative Advantages and Further Modification of the Bilirubin Excretion Test for Hepatic Function, *Am. J. M. Sc.* **192**:535 (Oct.) 1936.

2. Hanger, F. M.: The Flocculation of Cephalin-Cholesterol Emulsions by Pathological Sera, *Tr. A. Am. Physicians* **53**:148, 1938; Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, *J. Clin. Investigation* **18**:261 (May) 1939.

parenchymatous jaundice. It seemed plausible that a test denoting the presence of active damage to the liver might prove of greater clinical value, particularly in the diagnosis of mild and subclinical hepatic disease, than tests which measure the functional capacity of the liver as a whole. Accordingly, a study of the reliability of the flocculation test was undertaken, and the results obtained with a series of 155 selected subjects are recorded here.

MATERIAL

The subjects selected for study consisted of three groups: 1. Thirty-four patients manifesting irrefutable clinical evidence of disease of the liver. In this group there were 7 patients with acute hepatitis, 11 with portal cirrhosis (hypertrophic, 10; atrophic, 1); 1 with fatty metamorphosis (biopsy); 9 with long-standing chronic passive congestion secondary to congestive heart failure, and 6 with metastatic carcinoma (4 with extensive invasion of the liver). Eleven additional patients with obstructive jaundice proved by operation were included in this group, making a total of 45 patients. 2. Thirty-eight patients with a variety of diseases with symptoms and signs suggestive of mild chronic hepatic disease but requiring confirmatory studies. 3. A miscellaneous group of 72 persons selected at random in whose cases the routine histories and physical examinations disclosed no evidence of disease of the liver.

METHODS

Cephalin-Cholesterol Flocculation Test.—The method described by Hanger² was followed in every detail. A stock ether solution was prepared by dissolving 100 mg. of oxidized sheep brain cephalin³ and 300 mg. of cholesterol in 8 cc. of ether. An emulsion was then made by adding (slowly and with stirring) 1 cc. of the stock ether solution to 35 cc. of freshly distilled water which had been warmed to 65 or 70 C. The mixture was heated slowly to boiling and allowed to simmer until the final volume reached 30 cc. After cooling to room temperature, 1 cc. of the emulsion was added to a centrifuge tube containing 0.2 cc. of the patient's serum diluted with 4 cc. of physiologic (0.85 per cent) solution of sodium chloride. The mixture was thoroughly shaken, stoppered with cotton and allowed to stand undisturbed at room temperature. Readings were made after twenty-four and forty-eight hours, and the reactions were graded in terms of 0, plus-minus and 1 plus to 4 plus. A 4 plus reaction indicated complete flocculation leaving the supernatant liquid water clear. A plus-minus reaction designated only slight flocculation. It was found useful to set up an additional control tube containing 4 cc. of saline solution and 1 cc. of emulsion (without serum) to test the stability of the emulsion. Emulsions were prepared freshly on the day tested, and only carefully washed glassware was used. Serum which has been refrigerated for one day or longer may yield false positive flocculation reactions.

3. The cephalin used in this study was prepared by Dr. David Klein, of the Wilson Laboratories, Chicago. A difference in the reaction of various cephalin preparations was observed, depending on whether the cephalin was freshly prepared or had been exposed to the air for a number of weeks. On standing, cephalin is oxidized and assumes a dark brown color. False positive reactions may be avoided by use of the oxidized form of cephalin.

For confirmatory laboratory data in almost all cases the icterus index⁴ was determined; in some, the free and combined serum⁵ or blood⁶ cholesterol was measured, and in others, the bromsulphalein or the hippuric acid excretion test or both were done, depending on the cooperation of the subject. The technic used for the bromsulphalein test was similar to that described by Rosenthal and White⁷ except that 5 mg. of dye per kilogram of body weight⁸ was used and a single sample of blood was drawn thirty minutes after injection.⁹ Retention of more than 10 per cent was regarded as abnormal.¹ The oral hippuric acid test¹⁰ as modified by Kohlstaedt and Helmer¹¹ was employed except in cases of diarrhea or vomiting, in which the intravenous method¹² was substituted. With the oral method an excretion of 3 Gm. of hippuric acid (in terms of benzoic acid) was considered normal and 85 to 115 per cent of this value was set up as the normal range¹³; with the intravenous method 0.7 to 0.95 Gm. was regarded as normal. The hippuric acid test was omitted for all patients with elevated levels of nonprotein nitrogen in the blood. For 11 patients histologic examinations were made of the liver tissue obtained at operation (as far from the gallbladder bed as possible) or at necropsy. Whenever possible, more than one flocculation test was made of the same patient, but only differing results were incorporated in the tables. A diagnosis of chronic cholecystitis was recorded when the cholecystogram revealed significantly diminished concentration of the dye, although it was recognized that a poorly visualizing gallbladder may indicate failure of the excretory function of the liver rather than cholecystitis.

4. Newburger, R. A.: Determination of the Icteric Index by the Acetone Method, *J. Lab. & Clin. Med.* **22**:1192 (Aug.) 1937. Meulengracht, E.: Die klinische Bedeutung der Untersuchung auf Gallenfarbstoff im Blutserum, *Deutsches Arch. f. klin. Med.* **132**:285 (July) 1920.

5. Schoenheimer, R., and Sperry, W. M.: A Micromethod for the Determination of Free and Combined Cholesterol, *J. Biol. Chem.* **106**:745, 1934. Sperry, W. M.: A Micromethod for the Determination of Total and Free Cholesterol, *Am. J. Clin. Path.* **8**:91 (May) 1938.

6. Bloor, W. R., and Knudsen, A.: The Separate Determination of Cholesterol and Cholesterol Esters in a Small Amount of Blood, *J. Biol. Chem.* **27**:107, 1916.

7. Rosenthal, S. M., and White, E. C.: Clinical Application of Bromsulphalein Test for Hepatic Function, *J. A. M. A.* **84**:1112 (April 11) 1925.

8. O'Leary, P. A.; Greene, C. H., and Rowntree, L. G.: Diseases of the Liver: VIII. The Various Types of Syphilis of the Liver, with Reference to Tests for Hepatic Function, *Arch. Int. Med.* **44**:155 (Aug.) 1929. Robertson, W. E.; Swalm, W. A., and Konzelman, F. W.: Functional Capacity of the Liver: Comparative Merits of the Five Most Popular Tests, *J. A. M. A.* **99**:2071 (Dec. 17) 1932.

9. Soffer, L. J.: Present Day Status of Liver Function Tests, *Medicine* **14**:185 (May) 1935.

10. Quick, A. J.: The Synthesis of Hippuric Acid: New Test of Liver Functions, *Am. J. M. Sc.* **185**:630 (May) 1933.

11. Kohlstaedt, K. G., and Helmer, O. M.: A Study of the Hippuric Acid Excretion as a Test of Hepatic Function, *Am. J. Digest. Dis. & Nutrition* **3**:459 (Sept.) 1936.

12. Quick, A. J.: The Clinical Application of the Hippuric Acid and the Prothrombin Tests, *Am. J. Clin. Path.* **10**:222 (March) 1940.

13. Quick, A. J.: Clinical Value of the Test for Hippuric Acid in Cases of Disease of the Liver, *Arch. Int. Med.* **57**:544 (March) 1936.

TABLE 1.—*Cephalin-Cholesterol Flocculation Test of Patients with Unquestionable Disease of the Liver and Patients with Obstructive Jaundice*

Unquestionable Disease of the Liver and Patients with Obstructive Jaundice

Case	Age	Sex	Icterus Index		Cholesterol				Cephalin Flocculation Test		Brom-sul-phalein, %	Diagnosis	Comment
			Date	Units	Total, Mg. per 100 Cc.	Esters		Date	Result				
						Mg. per 100 Cc.	Per. centage						
1	52	M	4/11 5/ 4	160 30	182	132	27		4/11 5/ 6 5/13	+++ +++ ++	..	Toxic hepatitis (sulfanilamide)	Icteric 3 weeks; recovery
2	25	M	40	212	142	67		++++	..	Acute hepatitis	
3	36	M	5/28 6/19	17* 11*	159	112	70		5/28 6/19	+++ ++	..	Toxic hepatitis (sulfapyridine)	Icteric 8 days; hippuric acid, 1.31 Gm. (44%); recovery
4	44	F	84	250	105	42		+++	..	Acute hepatitis	Icteric 2 days; A/G, 3.3/4.2; recovery
5	36	F	40	179	111	62		+++	..	Acute hepatitis (operation)	Icteric 10 days; recovery
6	19	F	9	435	227	52		+++	..	Infectious mononucleosis with jaundice	Icteric 8 days; recovery
7	50	M	75	++	..	Acute atrophy (operation)	Subsiding icterus 4 days; recovery
8	48	M	20	114	68	60		+++	..	Atrophic portal cirrhosis; ascites	Icteric 1 week; A/G, 2.4/3.3; died on 3d day after admission
9	47	M	9*	171	92	53†		4/ 8 9/10	+++ ++	20	Hypertrophic portal cirrhosis	Hippuric acid, 2.64 Gm. (88%); im-proved on therapy
10	50	M	8*	177	104	59†		+++	15 (1 hr.)	Hypertrophic portal cirrhosis	Hippuric acid, 2.55 Gm. (85%)
11	60	F	10	296	204	69		+++	65	Hypertrophic portal cirrhosis	3.8/4.5 A/G, 3.0/4.3
12	57	M	3	112	69	62		++	..	Hypertrophic portal cirrhosis	Avitaminosis B; A/G, 3.0/4.3
13	65	F	7*	++	..	Hypertrophic portal cirrhosis	Chronic alcoholism
14	54	M	13*	164	98	61†		++	20	Hypertrophic portal cirrhosis	Pneumonia and uncontrolled diabetes
15	48	M	5	262	187	71		6/25 8/ 6	++	22	Hypertrophic portal cirrhosis	3 months before 1st test
16	67	M	6	+	0	Hypertrophic portal cirrhosis	Amebic typhlitis
17	50	M	3	±	40	Hypertrophic portal cirrhosis	Hippuric acid, 2.84 Gm. (95%)
18	54	M	9*	206	127	62		±	30	Hypertrophic portal cirrhosis
19	78	F	6	+	..	Hypertrophic portal cirrhosis	Chronic alcoholism
20	34	M	4	+	..	Hypertrophic portal cirrhosis	Pneumonia and uncontrolled diabetes
21	62	M	1		4/5 8/2	++	30	Chronic passive congestion	3 months before 1st test
22	67	M	4	+	..	Chronic passive congestion	Hippuric acid, 2.84 Gm. (95%)
									+	..	Chronic passive congestion
									+	..	Chronic passive congestion	Mild diabetes mellitus
									+	..	Chronic passive congestion	Wassermann and Kahn, 4 plus

RESULTS

1. *Patients with Acute or Chronic Disease of the Liver or with Obstructive Jaundice.*—The blood serums of all 7 patients with acute hepatitis, 9 of 11 patients with cirrhosis, 3 of 6 patients with carcinoma, 2 of 9 patients with chronic passive congestion and 1 patient with fatty metamorphosis of the liver produced prompt, strong flocculation reactions, ranging from 2 plus to 4 plus (table 1). The serums of 12 of the remaining 13 patients with chronic disease of the liver gave slight (plus-minus to 1 plus) flocculation reactions within twenty-four to forty-eight hours, and in 1 instance of carcinoma flocculation tests gave negative reactions. The 3 patients with carcinoma with strongly reacting serums revealed clinical signs of extensive hepatic involvement, and in 1 of these (case 30), biopsy disclosed intrahepatic cholangitis and diffuse swelling of the parenchymal cells, the last-mentioned changes apparently accounting for the strong flocculations. The patient with proved carcinoma whose serum produced negative reactions presented a slightly nodular right hepatic lobe. A decrease in the degree of flocculation ran parallel with the clinical improvement (cases 1, 3, 9, 16 and 20) and was found to be of prognostic significance.

No attempt at a comparative evaluation of the various tests of hepatic function was made in this study; nevertheless, it is of interest that the icterus index was normal for 19 of the 34 patients; the values for cholesterol esters were normal for 8 of 16 patients; bromsulphalein tests gave normal results for 2 of 15 patients, and the hippuric acid excretion was normal for 2 of 6 patients.

Of 11 patients with obstructive jaundice proved by operation, the blood serums of 8 produced only slight flocculation reactions within twenty-four to forty-eight hours (2, 1 plus; 6, plus-minus); 2 gave negative reactions, and 1 (in a case of advanced biliary cirrhosis) produced a prompt 3 plus reaction. It is not surprising that slight flocculations were obtained in so many of this group, for the duration of jaundice at the time of the flocculation tests ranged from two to eleven weeks and averaged six and one-half weeks. Moreover, biopsies of tissue from 3 of these 8 patients revealed focal necrosis of the polygonal cells with cholangitis in 2 and capillary cholangitis with proliferation of bile ducts and fatty metamorphosis in 1. In another patient mild chronic hepatitis was noted at operation. The 2 patients with negatively reacting serums presented histories of jaundice of only two and three weeks' duration respectively. In contrast to these observations, while the duration of icterus in 8 cases of parenchymatous jaundice ranged from two to twenty-one days, the average was only eight days, and prompt, strong flocculation reactions were obtained in all. Thus, flocculation tests may prove of value in differentiating obstructive from parenchymatous jaundice, prompt, strong reactions early in the course

of jaundice indicating a parenchymatous form of the disease, whereas either negative or slight flocculation reactions bespeak obstructive jaundice. This is best illustrated by the following cases.

CASE 1.—R. H., a white man aged 50, consulted his physician on Sept. 23, 1940, with the complaint of recurrent sharp epigastric pain radiating to both hypochondriac regions. The pains had begun on September 9, and four days later he had noted dark urine and pale stools. Jaundice had been first observed on September 21. His appetite had become poor, and he had lost 10 pounds (4.5 Kg.) in weight. He had undergone a cholecystectomy for gallstones twenty years previously and since then had been having occasional mild epigastric pain. Physical examination gave negative results except for moderate jaundice. The urine gave a 4 plus reaction for bile. The icterus index was 75 units. The provisional diagnosis was cholelithiasis with obstruction of the common duct. A sample of blood submitted for the cephalin-cholesterol flocculation test produced a 2 plus flocculation reaction, on the strength of which a diagnosis of acute hepatitis was suggested. Several days later the patient entered another hospital, where he was operated on soon afterward for obstructive jaundice. "A very small, shrunken liver ('acute atrophy') weighing approximately 300 Gm." was found, but there was no evidence of obstruction of the larger bile ducts.

The past history and the present illness were certainly suggestive of cholelithiasis with obstruction of the common duct. However, the cephalin flocculation test correctly indicated the true nature of the jaundice.

CASE 2.—M. M., a white man aged 40, a steel worker, entered the Michael Reese Hospital on May 5, 1940, with the complaint of painless progressive jaundice and clay-colored stools for two weeks. Coincidentally anorexia, nausea, occasional vomiting and dyspepsia were noted. There had been no abdominal pain. Examination revealed no abnormality except intense jaundice and a palpably enlarged nontender liver of increased consistency, palpable 5 cm. below the costal margin on inspiration. Urinalysis revealed: albumin, 1 plus; bile, 4 plus, and urobilinogen, 0. The stools were tan; they contained no bile and no blood. The icterus index was 120 units. The value for total serum cholesterol was 581 mg., and that for cholesterol esters, 97 mg., per hundred cubic centimeters (17 per cent). The value for serum phosphatase was 11.8 Bodansky units. Because of the high value for total cholesterol, a provisional diagnosis of obstructive jaundice had been made, but the low ester fraction, together with slight elevation in serum phosphatase, was presumptive evidence of parenchymatous damage. Blood was submitted for cephalin-cholesterol flocculation tests, which gave uniformly negative results. Accordingly, a final diagnosis of obstructive jaundice due to carcinoma of the head of the pancreas or to silent stone of the common duct was made, and operation was advised. At operation there were multiple stones in the common duct, a large stone in the ampulla of Vater and chronic cholecystitis.

CASE 3.—M. P., a white man aged 43, was admitted to the Michael Reese Hospital on May 30, 1940, complaining of recurrent attacks of epigastric pain with nausea and vomiting for eleven weeks. Chronic remittent jaundice had been present since the first painful seizure. Physical examination gave negative results

except for moderate icterus and tenderness in the right hypochondrium on pressure and on percussion with the fist. The icterus index was 40 units. The value for total serum cholesterol was 300 mg. and that for cholesterol esters 177 mg. per hundred cubic centimeters (59 per cent). The hippuric acid excretion was 0.77 Gm. in terms of benzoic acid (26 per cent). The value for serum phosphatase was 9.1 Bodansky units. Complete unanimity of opinion did not exist among the physicians in attendance, some holding that the depressed cholesterol esters and the low hippuric acid excretion indicated parenchymatous jaundice. Cephalin-cholesterol flocculation tests gave plus-minus reactions. Consideration of the onset, duration and degree of the jaundice correlated with the slight flocculation reactions led to the diagnosis of cholelithiasis with obstruction of the common duct. Operation on July 9 disclosed innumerable gallstones with thick grumous material filling the cystic, common and hepatic ducts. Chronic cholecystitis, and mild chronic hepatitis were present.

2. *Patients with Clinically Suspected Disease of the Liver.*—The 38 patients comprising this group had a variety of primary diseases (table 2). However, clinical evidence suggestive of chronic disease of the liver was common to all, though in some it was only through diligent search that the physical signs were elicited. In 37 cases analysis of the results of physical examination revealed one or more of the following symptoms: hepatic tenderness; pain on percussion with the fist over the right hypochondrium; tenderness in the right upper abdominal quadrant, and hepatic enlargement, most often slight, with or without splenic enlargement. In another case the presence of unexplained macrocytic anemia refractory to liver therapy suggested the possibility of disease of the liver. In all instances confirmatory diagnostic studies were necessary for a conclusive diagnosis. Included in this group were 7 patients whose symptoms had been diagnosed elsewhere as "nervous indigestion"; on 2 of these cholecystectomy had been performed previously, without benefit.

The cephalin-cholesterol flocculation test gave a positive reaction for all 38 patients, prompt, strong (2 to 3 plus) reactions having been obtained in 22 instances and slight (plus-minus to 1 plus) reactions in 16. In 30 patients one or more of the supplementary tests of hepatic function, such as the determination of the icterus index, the bromsulphalein test, the hippuric acid test or estimation of the cholesterol esters, disclosed damage to the liver, and in 2 of these further confirmation was found at operation. In 3 others biopsy disclosed histologic evidence of disease of the liver, making a total of 33 of the 38 patients in whose cases the suspicion of hepatic damage was confirmed by the flocculation test and by other means. It is noteworthy that even slight (plus-minus) flocculation reactions were significant of damage to the liver, for corroborative evidence was elicited from all 11 patients in this group. Of the remaining 5 patients, whose serums produced positive flocculation reactions but of whom adequate supplementary

TABLE 2.—Cephalin-Cholesterol Flocculation Test of Thirty-Eight Patients with Clinically Suspected Disease of the Liver

Case	Age	Sex	Icterus Index	Cephalin Flocculation Test		Bromsulph. alcoh. %	Hippuric Acid Excretion		Primary Diagnosis	Comment
				Date	Result		Gm.	%		
46	46	M	3	4/ 8	+++	5	0.27†	..	Diabetic acidosis	Punch tenderness in right upper quadrant (see text)
47	67	M	3	4/22	+	..	0.68	..	Chronic sepsis	Punch tenderness in right upper quadrant
48	42	M	5	+++	40	2.0	67	Bronchopneumonia	Tender liver; total cholesterol, 152; esters, 60%
49	48	F	8*	+++	..	2.15	72	Chronic hepatitis ?	Gallbladder removed (stones); tender liver 3 cm. from costal margin
50	42	F	3	+++	50	2.9	97	Chronic cholecystitis	Tender liver 3 cm. from costal margin; slightly increased consistency
51	38	F	4	+++	Chronic hepatitis	Unexplained dyspepsia; tender liver
52	56	F	16	+++	Acute cholecystitis	Operation; stones
53	53	M	4	+++	..	0.6†	..	Acute gout	Punch tenderness in right upper quadrant
54	26	M	+++	Bronchopneumonia	Tender liver 3 cm. from costal margin
55	37	M	4	+++	30	Duodenal ulcer	Tender liver
56	32	F	4	+++	20	Irritable colon	Marked tenderness in right upper quadrant
57	57	M	6	+++	Acute cholecystitis; stone	Biopsy: marked cloudy swelling; cholangitis
58	61	F	9	+++	30	Macrocytic anemia
59	40	F	7*	+++	30	3.41	111	Migraine	Unexplained dyspepsia; tender liver
60	28	M	13*	+++	40	Chronic hepatitis	Dyspepsia; remittent icterus 14 years
61	35	F	+++	5	3.39	113	Tertiary syphilis	Unexplained dyspepsia; palpable liver and spleen
62	27	M	3	4/26	+++	8	Stomach; hepatitis (operation)	Tender liver; biopsy, granuloma with regenerating liver tissue; granular degeneration of liver cells
63	55	M	5	6/12	±	Pernicious anemia; postero-lateral sclerosis	Intravenous dextrose 6/29-7/2
64	31	F	1*	6/19	+++	15	Chronic hepatitis ?	Gallbladder removed (stones); dyspepsia; tenderness in right upper quadrant
65	61	M	4	7/ 9	+++	25	Hyperthyroidism	Basal metabolic rate +47%; punch tenderness in right upper quadrant
66	76	M	4	+++	25	1.97	63	Atrophic cirrhosis ?	Ascites; receding liver; splenomegaly
67	50	F	25	+++	25	Stones; hepatitis	Operation
68	57	M	9*	+++	25	3.01	100	Chronic cholecystitis	Tender liver 3 cm. from costal margin
69	61	F	4	+	12	Chronic hepatitis	Tender liver 5 cm. from costal margin; splenomegaly
70	61	F	1	+	Chronic cholecystitis	Liver 6 cm. below xiphoid; irritable colon
71	53	F	11*	+	..	2.25	75	Chronic cholecystitis	Tender liver 2 cm. from costal margin
72	35	F	9*	+	13	Migraine	Unexplained dyspepsia; tenderness in right upper quadrant
73	57	M	4	±	8	2.97	59	Subacute cholecystitis; stones; hepatitis	Tender enlarged liver and spleen; biopsy, intracupillary cholangitis
74	51	F	4	±	20	Diabetes mellitus	Unexplained dyspepsia; tender liver
75	40	M	8	±	15	Chronic hepatitis ?	Firm liver; dyspepsia; gallbladder removed
76	28	F	±	20	2.48	82	Diabetes mellitus	Tender liver 1 cm. from costal margin
77	48	F	20*	±	20	Chronic hepatitis
78	40	F	7*	±	22	Chronic pelvic inflammation	Tender liver 1 cm. from costal margin
79	53	F	11*	±	22	Irritable colon	Punch tenderness in right upper quadrant; gallbladder dye: negative
80	35	M	12	±	25	Duodenal ulcer	Tender liver 4 cm. from costal margin; increased consistency
81	11	F	3	±	25	1.06	55	Tertiary syphilis	Liver 5 cm. from costal margin
82	56	F	6*	±	25	Atrophic gastritis	Unexplained tenderness in right upper quadrant
83	50	M	3	±	25	Chronic cholecystitis	Tender liver 3 cm. from costal margin

* Icterus index determined by Meulengraet method (normal, 4 to 6 units); all other icterus indexes, by Newburger acetone method (normal, 2 to 5 units).
† Intravenous hippuric acid tests.

tests could not be made for one reason or another, in 2 the liver was palpable and tender; in 1 it was moderately enlarged, and in 2 both the liver and the spleen were slightly enlarged.

Of the 33 cases of adequately confirmed disease of the liver bromsulphalein tests were performed in 24 but gave negative results in 4. The average retention of the dye in the cases in which abnormality was present was 24 per cent at the end of thirty minutes. Hippuric acid tests were conducted for 16 of these 33 patients, and in 8 of these tests the results were normal. From tables 1 and 2 it is apparent that the results of the cephalin-cholesterol flocculation test agreed more closely with the clinical picture than did those of any of the other tests of liver function.

The response to therapy was observed in 5 instances. Clinical improvement accompanied with a decrease in the flocculation reactions was noted in case 46 following a high carbohydrate diet and administration of insulin; in case 63, following intravenous administration of dextrose; in cases 56 and 62, following institution of a high carbohydrate, low fat diet, with adequate protein requirements derived largely from milk, eggs, dairy products and vegetables, together with whole vitamin B complex, and in case 65, following thyroidectomy.

The serum in case 53 produced a 3 plus flocculation reaction several days before an acute attack of gout, whereas three months later, in a stage of remission, the flocculation reaction was plus-minus. This observation is of interest and merits further investigation of the possible relation between the liver and acute gout, especially since it has been noted that high fat, low carbohydrate diets may precipitate an acute recurrence of gout.

The important role of the liver in disturbances of digestion and its participation in metabolic disorders are clearly exemplified by the following cases.

CASE 4.—G. S., a white woman aged 32, was seen on May 17, 1940, complaining of recurrent diarrhea for four years, severe epigastric cramps on arising in the morning and occasional bloating after meals. She had been receiving a bland diet and antispasmodics, without improvement. Physical examination gave negative results except for a spastic, nontender descending colon, a slightly tender ascending colon and considerable hypochondriac tenderness on the right on pressure and on percussion with the fist. Roentgen studies of the stomach, intestines and gallbladder revealed no abnormality except a spastic, irritable colon. Cultures and examinations of the stools gave negative results, as did analysis of the gastric contents. The diagnoses were: 1. Spasticity and irritability of the colon. 2. Probable chronic hepatitis. The cephalin-cholesterol flocculation reaction was 3 plus; the bromsulphalein test showed 20 per cent retention in thirty minutes. Therapy consisted of administration of vitamin B complex; a bland diet high in carbohydrate, low in fat and containing a maintenance content of protein, and calcium chloride. When seen eighteen days later she felt "swell," and only slight hypochondriac tenderness on the right side could be elicited. The cephalin-cholesterol flocculation reaction was 1 plus.

CASE 5.—J. R., a white man aged 27, was seen on April 25, 1940, complaining of cramping pains in the right upper abdominal quadrant for fifteen months, with loss of 14 pounds (6.4 Kg.) in weight. Extensive studies elsewhere had led to a diagnosis of "gallbladder irritation," and a bland, low fat diet was prescribed, without material benefit. Physical examination gave negative results except for a palpable, slightly firm, tender liver 1 cm. below the costal margin on deep inspiration. A cholecystogram revealed very poor concentration of the dye. The cephalin-cholesterol flocculation reaction was 2 plus. The diagnoses were: (1) chronic cholecystitis with probable cholelithiasis and (2) chronic hepatitis. Therapy similar to that in case 4 was prescribed, and progressive clinical improvement, with a gain of 10 pounds (4.5 Kg.) in weight, ensued. On July 9 the cephalin-cholesterol flocculation reaction was plus-minus. On August 30 there developed biliary colic followed by persistent low grade fever. Operation was performed on September 13. Cholesterosis of the gallbladder, a solitary cholesterol stone in the cystic duct and a nodular liver of increased consistency with perihepatitis were found. Biopsy of a nodule revealed granuloma with regenerating liver tissue and granular degeneration of the surrounding liver cells.

CASE 6.—H. C., a white man aged 46, entered the Michael Reese Hospital on April 5, 1940, complaining of excessive thirst, itching of the skin, weakness and loss of 30 pounds (13.6 Kg.) in one month. Physical examination gave essentially negative results except for slight punch tenderness over the liver and signs of ariboflavinosis. Urinalysis revealed: sugar, 4 plus; acetone, 2 plus. The dextrose content of the blood was 262 mg. per hundred cubic centimeters. The provisional diagnosis was diabetes mellitus with acidosis. The cephalin-cholesterol flocculation reaction was 3 plus on April 8, and on the following day the hippuric acid excretion (intravenous method) was 0.27 Gm. in terms of benzoic acid. Difficulty was encountered in controlling the glycosuria. Because of evidence of a hepatic factor, the diet was increased to 300 Gm. of carbohydrate, 100 Gm. of protein, and 120 Gm. of fat, and protamine zinc insulin, 60 units daily, was administered. The urine became free from sugar on April 20. On April 22 the cephalin-cholesterol flocculation reaction was 1 plus, indicating hepatic improvement. On May 10 the intravenous hippuric acid test revealed a normal excretion, 0.68 Gm. in terms of benzoic acid.

3. *Subjects with Unsuspected Disease of the Liver.*—This group (table 3) consisted of 12 "normal" adults and of 60 patients with miscellaneous diseases selected at random from the hospital wards and from the outpatient gastrointestinal department. No evidence of hepatic disease was apparent from the records of the routine histories and examinations. Blood specimens were obtained for routine cephalin-cholesterol flocculation tests, and all subjects with positive reacting serums were further investigated by more careful history taking, meticulous reexaminations, supplementary tests of liver function and, whenever possible, histologic or gross examinations of the liver.

Positive flocculation reactions were produced by the blood serums of 43 subjects (60 per cent), prompt, strong (2 plus to 4 plus) reactions having been obtained in 26 and slight (plus-minus to 1 plus) reactions in 17. In the remaining 29, the flocculation tests gave negative reactions. In 25 of the subjects with positive blood serums, one

TABLE 3.—*Cephalin-Cholesterol Flocculation Test of Seventy-Two Subjects with Unsuspected Disease of the Liver*

Case	Age	Sex	Icterus Index	Cephalin Flocculation Test	Bromsulph. alcin, %	Hippuric Acid Excretion		Primary Diagnosis	Comment
						Gm.	%		
84	62	M	2	++++	Syphilis; nephritis	Dyspepsia; nonprotein nitrogen, 80 mg. per 100 cc.
85	47	F	3	++++	Pyelocystitis	Twenty Gm. sulfanilamide
86	24	M	8*	++++	"Normal"	Nine months ago undiagnosed diarrhea for 6 weeks
87	43	M	10	++++	..	0.97†	...	Lobar pneumonia	Sulfapyridine; cholesterol, 111; esters, 60%
88	62	M	..	++++	..	3.54	118	Ulcerative colitis
89	28	M	14	++++	"Normal"	Recurrent diarrhea, abdominal pain, belching; total cholesterol, 199; esters 199 (63%)
90	61	M	20	++++	Atrophic gastritis	Antispyllitic therapy; neoursphenamine reaction
91	37	M	5	++++	..	2.01	67	Duodenal ulcer	Partial relief on ulcer therapy
92	37	M	5	++++	..	2.51	84
93	55	M	4	++++	Infectious mononucleosis	Liver 3 cm. from costal margin; increased consistency
94	31	M	..	++++	Ulcerative colitis	Autopsy: peritoneal fibrosis; increased consistency
95	35	F	7*	++++	Chronic nephritis	Advanced glomerulonephritis
96	56	M	2	++++	5	Atrophic gastritis	Punch tenderness in right upper quadrant; spastic colon
97	56	F	2	++++	Acute nephritis	Abnormal dextrose tolerance
98	43	M	13	++++	Hypothyroidism	Basal metabolic rate, +53.0%
99	37	F	..	++++	30	3.14	105	"Postoperative recovery"	Cholecystectomy for stones 3 months previously
100	25	M	6	++	40	Irritable colon	Tender liver 3 cm. from costal margin; punch tenderness
101	34	M	10	++	10	"Normal"	No complaints
102	30	F	9*	++	15	2.77	92	Cholelithiasis	One year ago, icterus for 1 week
103	53	F	9*	++	17	Chronic cholecystitis	Tender liver 2 cm. from costal margin
104	33	F	5*	++	15	Stones; cholecystitis	Tender liver 2 cm. from costal margin
105	24	M	6	++	22	3.13	104	Chronic cholecystitis	Tender liver 2 cm. from costal margin
106	56	F	..	++	"Normal"
107	21	M	..	++	15	2.83	94	Hyperthyroidism	Malaria 5 to 8 years as child; gastrointestinal symptoms 4 years
108	16	M	1	++	Chronic nephritis	Basal metabolic rate, +42.6%
109	35	F	6	++	Infectious mononucleosis	Uremia
110	20	M	2	+	5	1.09	26	Cholelithiasis
111	61	M	3	+	5	1.90	66	Lymphosarcoma (operation)	Biopsy: marked cloudy swelling; pigment granules
112	42	F	3	+	23	3.45	115	Diabetes mellitus	Gastric; extension to liver; perihepatitis
113	57	M	12	+	20	Recurrent stones
114	31	F	..	+	..	1.42	47	Fernicious anemia
115	..	M	2	+	3	1.54	52	Undiagnosed duodenal ulcer	Previous cholecystectomy
									Unexplained abdominal pain; tenderness in right upper quadrant
									Extensive antispyllitic therapy

116	69	F	4	±	25	Irritable colon	Attacks of nausea and vomiting
117	57	F	..	±	Hyperthyroidism	Basal metabolic rate, +22.5%
118	23	M	6	±	"Normal"	Nausea and vomiting after fatty foods
119	22	M	2	±	10	0.74†	...	Ulcerative colitis	Total cholesterol, 163; esters, 101 (62%)
120	41	M	3	±	..	1.88	63	Tabes dorsalis	Gastric crises
121	65	M	14	±	18	2.23	74	Chronic arthritis	...
122	54	M	..	±	5	3.81	127	Undiagnosed	"Tender liver 1 cm. from costal margin; dizzy; headaches
123	19	F	6	±	10	"Normal"	Recurrent nausea; distress after meals; belching
124	38	F	..	±	Chronic cholecystitis	"Tender liver 1 cm. from costal margin"
125	65	M	6	±	Fernicious anemia	Postero-lateral sclerosis
126	67	F	6	±	22	3.22	107	Duodenal ulcer	Gallbladder removed (stones) in past; tender liver
127	43	F	2	±	Cholelithiasis	Operation: normal liver
128	62	F	..	0	Diabetes mellitus	...
129	30	F	..	0	5	Diabetes mellitus	...
130	72	F	3	0	Diabetes mellitus	...
131	38	F	..	0	Diabetes mellitus	...
132	60	F	..	0	Diabetes mellitus	...
133	49	F	6	0	Atrophic gastritis	...
134	50	M	..	0	Duodenal ulcer	...
135	57	M	..	0	Duodenal ulcer	...
136	59	M	..	0	Duodenal ulcer	...
137	45	M	..	0	Asymptomatic	Ancient perforated duodenal ulcer
138	49	F	..	0	Chronic cholecystitis	Treated; asymptomatic
139	35	F	5	0	Chronic cholecystitis	Mild involvement
140	49	M	5	0	Gastric resection	...
141	61	M	4	0	Chronic gout	...
142	45	F	2	0	Multiple sclerosis	...
143	54	M	6	0	Gastric carcinoma	...
144	60	F	4	0	Neurosis	...
145	26	F	4	0	Irritable colon	...
146	44	M	..	0	Irritable colon	...
147	41	M	4	0	Neurosis	...
148	35	F	..	0	Neurosis	...
149	59	M	5	0	Neurosis	...
150	27	M	4	0	Normal	...
151	27	F	4	0	Normal	...
152	28	M	..	0	Normal	...
153	35	M	5	0	Normal	...
154	45	M	..	0	Normal	...
155	62	F	..	0	Normal	...

* Icterus index determined by Meulengraecht method (normal, 4 to 6 units); all other icterus indexes, by Newburger acetone method (normal, 2 to 5 units).
† Intravenous hippurate field tests.

or more supplementary tests of liver function revealed abnormalities, and in 3 others confirmatory evidence of disease of the liver was found at operation, necropsy or biopsy. Thus, in a total of 28 (65 per cent) of the 43 positive flocculation reactions the diagnosis was further established by other means. It is clinically significant that 5 of these 28 subjects had regarded themselves as normal, healthy adults. Here again it may be noted that a bromsulphalein test was performed in 21 of the confirmed cases and the excretion was normal in 6, the average dye retention in the abnormal cases being 24 per cent at the end of thirty minutes. The hippuric acid test was normal in 8 of 16 confirmed cases.

In the cases of the remaining 15 patients with positive flocculation reactions, in which for one reason or another adequate confirmatory studies could not be made, further clinical study disclosed a history of dyspepsia in 2, hepatic tenderness or enlargement in 4, sulfanilamide (20 Gm.) therapy in 1, hyperthyroidism in 3, ulcerative colitis in 1, glomerulonephritis in 2, infectious mononucleosis in 1 and pernicious anemia with involvement of the cord in 1.

The significance of these surprising results and their implications may be demonstrated more vividly by a brief presentation of the following reports.

CASE 7.—I. W., a white man aged 28, a physician, who had regarded himself as a healthy, normal person, submitted blood to be used in this study as a normal control. The cephalin-cholesterol flocculation reaction was 3 plus in twenty-four hours. Four days later another sample of blood again produced a 3 plus flocculation reaction. Further investigation revealed in retrospect a history of frequent belching, recurrent abdominal cramps with diarrhea for two years and a sallow complexion for several years. Examination disclosed subicteric scleras and slight tenderness to percussion with the fist over the liver. The icterus index was 14 units. The value for total serum cholesterol was 199 mg. and that for cholesterol esters 126 mg. per hundred cubic centimeters (63 per cent). The bromsulphalein test showed 30 per cent retention in thirty minutes. The cholecystogram was normal. Approximately two weeks later, while on a vacation, he became visibly jaundiced, and two weeks thereafter the icterus index was 20 units. His scleras are still subicteric, and the most recent flocculation reaction was 1 plus. The diagnosis was mild acute hepatitis, probably representing an acute exacerbation of a preexisting subclinical chronic hepatitis.

CASE 8.—M. K., a white man aged 66, had been receiving ambulatory treatment for a roentgenographically proved chronic duodenal ulcer. Although the pain of the ulcer had been relieved thereby, he complained of persistent heartburn and regurgitation of sour material shortly after meals. Physical examination, gastroscopic study and roentgenograms of the stomach, intestines and gallbladder failed to reveal any abnormality. A routine cephalin-cholesterol flocculation reaction was 3 plus. The icterus index was 5 units. The hippuric acid excretion was 2.51 Gm. (84 per cent) in terms of benzoic acid. The diagnosis was mild chronic hepatitis. Appropriate therapy, including administration of vitamin B complex, resulted in symptomatic improvement and a reduction in the flocculation reaction to 1 plus.

CASE 9.—N. G., a Negro aged 37, had been under treatment for "irritable colon." The reaction to a routine cephalin-cholesterol flocculation test was 2 plus. Further inquiry elicited a history of frequent nausea, and careful reexamination revealed a tender liver palpable 4 cm. below the costal margin in the midclavicular line on inspiration. Roentgen studies gave negative results except for an irritable colon and fair concentration of the dye in the gallbladder. Gastroscopic examination revealed no abnormality. The bromsulphalein test showed 30 per cent retention in thirty minutes. The added diagnosis was mild chronic hepatitis. It becomes apparent from these results that the diminished visualization of the gallbladder may possibly have resulted from the impaired excretory function of the liver rather than from disease of the gallbladder.

CASE 10.—S. S., a white man aged 43, had undergone a cholecystectomy for cholelithiasis and chronic cholecystitis three months previously and was feeling "fine." Physical examination gave negative results. The reaction to a routine cephalin-cholesterol flocculation test was 3 plus. The bromsulphalein test showed 30 per cent retention in thirty minutes. The icterus index was 13 units. The diagnosis was subclinical chronic hepatitis.

CASE 11.—H. W., a white man aged 61, had for four years received hospital and outpatient care because of recurrent nausea and "burning" and tenderness in the epigastrium. Exhaustive studies gave negative results except for gastroscopic evidence of advanced, diffuse atrophic gastritis. As studies of liver function had not been made, a routine cephalin-cholesterol flocculation test was performed, and a 3 plus reaction was obtained. The hippuric acid excretion three days later was 2.01 Gm. (67 per cent) in terms of benzoic acid. The icterus index was 4 units. Further inquiry at this time disclosed a history of severe dermatitis in 1933, following sixteen injections of neoarsphenamine for syphilis and requiring multiple blood transfusions; there had been no manifest jaundice. The added diagnosis was subclinical chronic hepatitis secondary to arsphenamine intoxication.

It is evident from these observations and from table 3 that mild and subclinical disease of the liver is much more common than is generally appreciated or clinically recognized. Indeed, the importance of this unexpected finding and the consequent need of more careful study specifically directed toward the early diagnosis of disease of the liver cannot be overemphasized, for it is only in this stage that appropriate therapy may most successfully arrest the pathologic process and effect a restitution of normal function.

COMMENT

In this study the cephalin flocculation reaction was found to be positive in the serum of all patients with acute hepatitis, cirrhosis and chronic passive congestion of the liver, whereas in the serum of patients with hepatic carcinoma the reaction seemed to be related to the extent of malignant involvement. It was further observed that clinical improvement was accompanied with a decrease in the flocculation reaction. Of the patients with obstructive jaundice, flocculation reactions were negative in the serums of only 2 and slight in those of the majority.

In 4 of the latter evidence of disease of the liver was demonstrable, and in 1 patient with a strongly flocculating serum advanced biliary cirrhosis was found. Hanger² reported negative flocculation reactions for 10 of 46 patients with cirrhosis, for all of 13 patients with chronic passive congestion and for 21 of 25 patients with obstructive jaundice, but such divergent results are not inconsistent, for the degree of active damage to the liver associated with these disorders may vary in different persons or at different times in the same person. From the present study it is believed that the flocculation test may be of distinct value in differentiating obstructive from parenchymatous jaundice, either a negative or a slightly positive reaction indicating the obstructive form. Strongly positive reactions early in the course of jaundice point to a parenchymatous form of the disease whereas in the presence of long-standing jaundice they may not be of differential value owing to extensive secondary hepatic damage. Attention must be directed to a form of postarsphenamine jaundice recently described by Hanger and Gutman,¹⁴ which is associated with a negative flocculation reaction and which is believed to be due to intrahepatic biliary obstruction rather than to parenchymatous changes.

For a number of years it has been a routine procedure of mine to search diligently in all patients for symptoms and signs suggestive of hepatic disease. Consequently the results recorded for the 38 patients with clinically suspected disease of the liver are of particular interest, for the flocculation reactions were positive for all. In 33 the diagnosis was confirmed by other means, and in the remaining 5, presumptive clinical evidence had been elicited. These data not only indicate the reliability of the flocculation test but clearly demonstrate the importance of more careful and intensive bedside study. Indeed, in 1933, Chapman, Snell and Rowntree¹⁵ observed "that careful examination in so-called latent cases (of cirrhosis) may elicit symptoms and signs at some time in the course of the disease." More recently, Bloomfield¹⁶ echoed this thought when he stated that if physical examinations were made earlier, signs of insidious hepatic lesions probably could be detected in many persons before the advanced stage of cirrhosis is reached.

The striking number of persons with unsuspected disease of the liver as revealed by the routine use of the cephalin flocculation test is testi-

14. Hanger, F. M., and Gutman, A. B.: Postarsphenamine Jaundice Apparently Due to Obstruction of Intrahepatic Biliary Tract, *J. A. M. A.* **115**:263 (July 27) 1940.

15. Chapman, C. B.; Snell, A. M., and Rowntree, L. G.: Compensated Cirrhosis of the Liver: A Plea for More Intensive Consideration of the Earlier Stages of Disease of the Hepatic Parenchyma, *J. A. M. A.* **100**:1735 (June 3) 1933.

16. Bloomfield, A. L.: The Natural History of Chronic Hepatitis (Cirrhosis of the Liver), *Am. J. M. Sc.* **195**:429 (April) 1938.

mony that the incidence of mild and subclinical hepatic disease is higher than is generally appreciated today and that a meticulous clinical search for its presence should be made in all patients under observation. Moreover, unless a confirmatory test of damage to the liver is incorporated as a routine procedure in the study of digestive disorders, just as the cholecystogram or gastric analysis is today, hepatic disease in many cases is likely to remain unrecognized until irreversible functional changes have ensued. Since the cephalin-cholesterol flocculation test is a simple, sensitive test which can be performed simultaneously and expeditiously on a large number of serums, it is advocated as an ideal routine test for active disease of the liver.

Finally, although the exact nature of the flocculating substance present in the serums of patients with disease of the liver is unknown, it has been suggested¹⁷ that the underlying mechanism is dependent on the adsorption of a quantitatively altered globulin constituent by the cephalin-cholesterol particles. Further studies, however, are necessary for a proper understanding of the various factors concerned.

SUMMARY AND CONCLUSIONS

The results obtained with the cephalin-cholesterol flocculation test in a study of 155 persons are reported.

The cephalin-cholesterol flocculation test is a reliable, sensitive test of active damage to the liver, possessing prognostic value.

It is useful in the early diagnosis of obstructive and parenchymatous jaundice, negative or slight flocculation reactions indicating obstructive jaundice and prompt, strong flocculation reactions denoting parenchymatous jaundice.

The results of routine cephalin-cholesterol flocculation studies in an unselected group of patients indicate that mild and subclinical disease of the liver occurs more frequently than is generally appreciated and unless specifically sought may elude recognition. It is proposed that a test of liver function be incorporated as an integral part of the study of all patients with digestive disorders.

Because of its simplicity, the cephalin-cholesterol flocculation test is advocated as an ideal routine test for active disease of the liver.

ADDENDUM

Since the preparation of this paper, Pohle and Stewart¹⁸ have reported similar observations indicating that the cephalin-cholesterol flocculation

17. Hanger, F. M.: Personal communication to the author.

18. Pohle, F. J., and Stewart, J. K.: The Cephalin-Cholesterol Flocculation Test as an Aid in the Diagnosis of Hepatic Disorders, *J. Clin. Investigation* **20**:241 (March) 1941.

test is a sensitive and reliable index of disease of the liver. Further, they observed positive flocculation reactions in 18 of 23 cases of obstructive jaundice and concluded that the flocculation test is "not a reliable guide" in the differential diagnosis of obstructive and parenchymatous jaundice. It is evident that the results of the flocculation test in cases of obstructive jaundice depend on the amount of associated damage to the hepatic parenchyma. Hence the cephalin flocculation test may prove more reliable if either slight or negative flocculation reactions are regarded as indicative of obstructive jaundice, particularly if the patients are seen early in the course of the disease.

ROLE OF THE ADRENAL GLANDS IN SHOCK

VALUE OF DESOXYCORTICOSTERONE ACETATE IN THE PREVENTION OF OPERATIVE SHOCK

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There is considerable evidence to substantiate the postulate that the adrenal cortex acts as a protective mechanism against the development of many of the so-called states of shock. Adrenalectomy produces a state of shock. Normal health and vigor under ordinary conditions may be maintained in adrenalectomized dogs by injections of adrenal cortical extract. However, these dogs have circulatory collapse following any stimulus which puts a strain on the organism.¹ Certain investigators have called attention to the similarity of the signs and symptoms of adrenal insufficiency and those of secondary or traumatic shock and have suggested that the latter may be due to failure of adrenal cortical function.¹ Selye and his co-workers² have reported that one of the tangible evidences of the organism's attempt to combat shock is found in their studies, which showed increased activity of the adrenal glands during recovery from shock. Weil and Browne³ found unusually large quantities of adrenal cortical hormone in the urine of patients who underwent various surgical procedures and in other patients subject to stimuli of the shock-producing type. Selye and his collaborators² found characteristic pathologic changes in the adrenals in the presence of traumatic shock. The weight and size of these glands were found to have increased, and the cortical cells were greatly enlarged and showed evidence of having discharged their lipid granules. These changes were found to follow shock produced by many types of

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Desoxycorticosterone acetate for this study was supplied by Drs. G. Stragnell and E. Schwenk, of the Schering Corporation, Bloomfield, N. J.

Dr. Adelaide P. Barer, of the Department of Medicine, carried out the hemoglobin determinations by means of a Klett Sumsnerson photoelectric colorimeter.

1. Swingle, W. W.; Parkins, W. M.; Taylor, A. R., and Hays, H. W.: A Study of the Circulatory Failure and Shock Following Trauma to the Healthy Vigorous Adrenalectomized Dogs, *Am. J. Physiol.* **124**:22, 1938.

2. Selye, H.; Dosne, C.; Bassett, L., and Whittaker, J.: On the Therapeutic Value of Adrenal Cortical Hormones in Traumatic Shock and Allied Conditions, *Canad. M. A. J.* **43**:1, 1940.

3. Weil, P., and Browne, J. S. L.: The Excretion of Cortin After Surgical Operations, *Science* **90**:445, 1939.

stimuli, such as overdosage of drugs, exposure to cold, fractures and peritoneal lesions. This extends and corroborates the data of Zwemer⁴ and those of Wohl and his associates,⁵ who also found evidence of pathologic changes in the adrenal cortex in other conditions associated with circulatory collapse.

Although extensive knowledge concerning the functions of the adrenal cortex is lacking, certain functions have been studied. There is considerable evidence that the adrenal cortical hormone has governing powers over the following factors: (a) electrolyte balance, particularly the balance between the sodium and the potassium ions;⁶ (b) circulating plasma volume,⁷ and (c) capillary permeability.⁸ Since increased capillary permeability is present in certain phases of surgical shock, the work of Menkin on the relation of adrenal cortical extract to such permeability is of particular interest. Menkin⁸ reported that the increase in capillary permeability caused by inflammatory exudates can be wholly or in part inhibited by the local injection of adrenal cortical extract. The criterion of permeability is the degree of permeation of the capillary wall by trypan blue. A preliminary observation with desoxycorticosterone acetate indicated a similar inhibitory tendency on capillary permeability. There is evidence that the adrenal cortical hormone antagonizes both insulin hypoglycemia and epinephrine hyperglycemia⁹ and is interrelated with activities of other endocrine glands.¹⁰ Since there apparently are many functions of the adrenal cortex, it is not surprising that cortical preparations have been used in the treat-

4. Zwemer, P. L.: Study of Adrenal Cortex Morphology, *Am. J. Path.* **12**: 107, 1936.

5. Wohl, M. G.; Burns, J. C., and Clark, J. H.: Adrenal Glands in Dogs with High Intestinal Obstruction, *Proc. Soc. Exper. Biol. & Med.* **33**:543, 1936.

6. Thorn, G. W.; Barbutt, H. R.; Hitchcock, F. A., and Hartman, F. A.: Effect of Cortin upon Renal Excretion of Sodium, Potassium, Chloride, Inorganic Phosphorus and Total Nitrogen in Normal Subjects and in Patients with Addison's Disease, *Endocrinology* **21**:213, 1937.

7. (a) McAllister, F. F., and Thorn, G. W.: Effect of Adrenal Cortical Hormone on Reduction of Plasma Volume Resulting from Etherization, *Proc. Soc. Exper. Biol. & Med.* **36**:736, 1937. (b) Fine, J.; Fuchs, F., and Mark, J.: Effect of Desoxycorticosterone on Plasma Volume in Intestinal Obstruction, *ibid.* **43**: 514, 1940. (c) Ragan, C.; Ferree, J. W., and Fish, G. W.: Effect of Desoxycorticosterone Acetate upon Plasma Volume in Patients During Ether Anesthesia and Surgical Operations, *ibid.* **42**:712, 1939.

8. Menkin, V.: Effect of Adrenal Cortex Extract on Capillary Permeability, *Am. J. Physiol.* **129**:691, 1940.

9. Selye, H., and Dosne, C.: Inhibition by Cortin of Blood Sugar Changes Caused by Adrenalin and Insulin, *Proc. Soc. Exper. Biol. & Med.* **42**:580, 1939.

10. Selye, H.: Thymus and Adrenals in Response of Organism to Injuries and Intoxications, *Brit. J. Exper. Path.* **17**:234, 1936. Selye and others.²

ment of many conditions. Adrenal cortical therapy is well established in the treatment of Addison's disease, and this use of the treatment will not be discussed further. Beneficial effects have been reported in cases of anaphylaxis,¹¹ intoxication due to intestinal obstruction,¹² intoxication due to potassium,¹³ various infectious diseases,¹⁴ burns¹⁵ and surgical shock.¹⁶ The fact that adrenal cortical therapy is of reported value in such a diversity of conditions led Selye to suggest that it is "rather likely that the hormone is not a specific antidote in any one of these conditions but raises shock resistance in general because a condition of 'relative adrenal insufficiency' exists in organisms exposed to non-specific damage."²

This paper is chiefly concerned with adrenal cortical therapy in relation to surgical shock. There is considerable experimental work to suggest that adrenal cortical preparations are of value in the treatment of this condition. Heuer and Andrus^{12b} produced shock in dogs by intravenous injection of aqueous extracts of the contents of obstructed intestines. Control dogs did not recover from the shock thus produced, and intravenous transfusions of blood or saline solution brought about only temporary improvement. However, when adrenal cortical extract

11. Wolfram, J., and Zwemer, R. L.: Cortin Protection Against Anaphylactic Shock in Guinea Pigs, *J. Exper. Med.* **61**:9, 1935.

12. (a) Wohl, M. G.; Burns, J. C., and Pfeiffer, G.: High Intestinal Obstruction in the Dog Treated with Extract of Adrenal Cortex, *Proc. Soc. Exper. Biol. & Med.* **36**:549, 1937. (b) Heuer, G. J., and Andrus, W. De W.: Effect of Adrenal Cortical Extract in Controlling Shock Following Injection of Aqueous Extracts of Closed Intestinal Loops, *Ann. Surg.* **100**:734, 1934.

13. Zwemer, R. L., and Truskowski, R.: Importance of Corticoadrenal Regulation of Potassium Metabolism, *Endocrinology* **21**:40, 1937.

14. Pottenger, F. M.: Neural and Endocrine Factors in Bodily Defense, *Endocrinology* **21**:449, 1937.

15. Wilson, W. C.; MacGregor, A. R., and Stewart, C. P.: The Clinical Course and Pathology of Burns and Scalds Under Modern Methods of Treatment, *Brit. J. Surg.* **25**:826, 1938. Wilson, W. C., and Stewart, C. P.: Changes in Blood Chemistry After Burning Injuries and in Other Grave Surgical Conditions, with Some Reference to Treatment by Desoxycorticosterone Acetate, *Edinburgh M. J.* **46**:153, 1939.

16. (a) Weil, P. G.; Rose, B., and Browne, J. S. L.: The Reduction of Mortality from Experimental Traumatic Shock with Adrenal Cortical Substances, *Canad. M. A. J.* **43**:8, 1940. (b) Selye, H., and Dosne, C.: Treatment of Wound Shock with Corticosterone, *Lancet* **2**:70, 1940. (c) Reed, F. R.: Acute Adrenal Cortex Exhaustion and Its Relationship to Shock, *Am. J. Surg.* **40**:514, 1938. (d) Scudder, J.: Shock: Blood Studies as a Guide to Therapy, Philadelphia, J. B. Lippincott Company, 1940. (e) Perla, D.; Freiman, D. C.; Sandberg, M., and Greenberg, S. S.: Prevention of Histamine and Surgical Shock by Cortical Hormone and Saline, *Proc. Soc. Exper. Biol. & Med.* **43**:397, 1940. (f) Northrup, L. C.: Adrenal Cortex in Surgery, *J. Oklahoma M. A.* **32**:83-84, 1939.

was given with the transfusion the blood pressure returned to a level near normal and the lives of the animals were prolonged. Perla and his co-workers^{16e} reported that adrenal cortical extract and desoxycorticosterone when given with saline solution were efficacious in preventing and in treating histamine shock in rats. It has been previously stated that the adrenal cortical hormone is concerned with the regulation of circulating plasma volume. A decreased circulating plasma volume is invariably associated with surgical shock. Certain anesthetic agents, particularly ether, cause such a decrease. McAllister and Thorn^{7a} found that in dogs this decrease could be prevented by large intravenous doses of adrenal cortical extract. Ragan and his associates^{7c} reported that the administration of desoxycorticosterone acetate three or four hours before operation prevented a decrease in plasma volume in a group of patients on whom urologic operations were performed with ether anesthesia. In control cases there was a decrease in plasma volume from 3 to 8 per cent. Fine and his co-workers^{7b} found that the fall in plasma volume observed in dogs subjected to distention of the small intestine could be diminished by the administration of desoxycorticosterone acetate but that survival was not significantly increased.

In spite of the evidence which has accumulated in the experimental laboratories concerning the value of cortical therapy in the treatment or prevention of shock, there are few reports concerning the clinical application of this work. Wilson and his associates¹⁵ reported favorable results from the use of adrenal cortical extract in the treatment of shock in cases of extensive burns. Reed^{16c} gave adrenal cortical extract to 50 patients undergoing various gynecologic and general surgical procedures. His clinical impression was that these patients were definitely resistant to shock, and in several instances in which shock had occurred the cortical extract was of great value in conjunction with intravenous fluids and transfusion. Perla^{16e} gave desoxycorticosterone acetate to 12 patients whom he considered poor risks, and his impression was that these patients did unusually well; in none of them did shock develop. Desoxycorticosterone was given for several days before operation, in conjunction with sodium chloride.

It is exceedingly difficult to determine the value of any therapeutic measure in preventing the shock associated with clinical operative procedures. The factors that produce shock under these conditions, i. e., hemorrhage, tissue trauma, neurogenic reflexes and depth and type of anesthesia, vary markedly from case to case. The resistance of the patients varies tremendously, since this is dependent on the states of dehydration and nutrition, the degree of anemia and other factors.

In the general surgical service of the University Hospital, 72 patients have been given desoxycorticosterone acetate preoperatively. This substance is absorbed in such a manner that the maximum effect

TABLE 1.—*Value of Desoxycorticosterone in the Prevention of Operative Shock*

THORACIC OPERATIONS						Blood Loss, Cc.		
	Cases	Anesthetic Shock	Surgical Shock	Latent Shock		No Shock	Shock	
Thorneoplasty								
Treated patients.....	20	1	8 (40%)	0	Maximum	754	994	
					Minimum	330	483	
					Average	470	708	
Controls.....	22	2	10 (43%)	0	Maximum	610	919	
					Minimum	200	326	
					Average	422	600	
(3 patients in each group had received intravenous fluids; 1 in group treated with desoxycorticosterone had shock)								
Lobectomy and pneumonectomy								
Treated patients.....	3	0	2 (66%)	0		1	1 920	
						3 570	2 820	
Controls.....	3	1	2 (66%)	0		2 550	1 620	
							3	
RADICAL MASTECTOMY						Blood Loss, Cc.		
Treated patients.....	10	0	3 (33%)	0	Maximum	695	(7 cases in-	
					Minimum	390	cluding all	
					Average	560	cases of	
(1 additional patient was given intravenous fluids because of increased pulse rate)								
Controls.....	5	0	2 (40%)	1	Maximum	640		
					Minimum	350		
					Average	480		
ABDOMINAL OPERATIONS						Blood Loss, Cc.	Hemo-concentration	
	Cases	Anes- thetic Shock	Surgical Shock	Latent Shock				
Gastric resection								
Treated patients.....	6	1	0	0	Maximum	370	15%	
					Minimum	120	4%	
					Average	260	6%	
Controls.....	5	1	1	0	Maximum	500	17%	
					Minimum	210	4%	
					Average	310	7%	
Operation for intestinal conditions								
Treated								
Resection.....	6	1	1	0	Maximum	340	10%	
Operation for fecal fistula.....	3	0	1	0	Minimum	82	3%	
Operation for ventral hernia....	2	0	0	0	Average	180	5%	
Mikulicz procedure.....	5	0	1	0				12 cases 8 cases
Exploratory laparotomy, ap- pendectomy.....	1	1	0	0				(Includes all cases of shock)
	17	2	3 (17%)	0				
Controls								
Resection.....	5	0	1	0	Maximum	300	13%	
Operation for fecal fistula.....	3	1	1	0	Minimum	90	3%	
Operation for ventral hernia....	2	0	1	0	Average	190	6%	
Mikulicz procedure.....	4	0	0	0				6 cases 5 cases
	14	1	3 (21%)	0				(Includes all cases of shock)
(Duration of anesthesia, 1½ hours or longer in each case)								
Colectomy						Intravenous Fluids Necessary During Operation		
Treated patients.....	4	1	1 (25%)	0		3 (75%)		
Controls.....	7	1	2 (28%)	0		4 (57%)		
ABDOMINOPERINEAL RESECTION						Total Number with Shock	Blood Loss, Cc.	
	Cases	Anes- thetic Shock	Shock in Abdom- inal Part	Shock in Perineal Part	Shock on Return Moderate Severe			
Treated patients	12	1	1	4 (33%)	3 (25%) 0	6 (60%)	12 cases	
							Maximum	500
							Minimum	200
							Average	380
Controls.....	12	0	1	5 (40%)	2 (16%) 1 (8%)	7 (59%)	6 cases	
							Maximum	781
							Minimum	234
							Average	420

is obtained between four and twelve hours after injection.¹⁷ Thus, in order to have a maximum level at the time of operation, injections were given twelve, six and four hours before operation. Five or ten milligrams was given at each intramuscular injection. This routine was followed for the thoracoplasty, lobectomy, radical mastectomy and gastrectomy. In addition to this divided preoperative dose, 5 mg. was given twice daily for two days to patients on whom intestinal operations and abdominoperineal resections of the rectum were performed. With few exceptions these patients were given intravenous injections of physiologic solution of sodium chloride varying between 1,000 and 3,000 cc. for two or three days before operation. It was not thought advisable to give desoxycorticosterone acetate over a long period before operation because of the possibility that this procedure might cause atrophy of the adrenal cortex.^{17a} Selye² recently has found evidence to substantiate this possibility.

In order to obviate as many variables as possible, these cases were placed in groups for comparison on the basis of type of operation. The

TABLE 2.—*Comparative Data*

Total number of treated patients.....	72
Total number of treated patients in whom shock developed.....	23 (31%)
Total number of control subjects.....	68
Total number of control subjects in whom shock developed.....	27 (39%)

amount of hemoglobin lost at operation was determined from the sponges, drapes, etc., and by comparison with the original hemoglobin level the quantity of blood lost was determined. The results for the treated patients and for the controls are shown in tables 1 and 2. Space does not permit an analysis of such factors as the plane of anesthesia, the duration of the operation and the determination of the probable cause of shock in each case. However, it is felt that sufficient data are given to support the conclusion that desoxycorticosterone acetate given preoperatively in the doses cited had little significant effect in preventing shock associated with these general surgical procedures as compared with control groups. The criterion of surgical shock was arbitrarily established as a state in which the blood pressure was below 80 systolic and 60 diastolic and the associated pulse rate was above 115. In both the treated and the untreated patients shock was usually not severe

17. Thorn, G. W.: Personal communication to the author.

17a. Recent communications from other investigators have revealed that much larger doses of desoxycorticosterone acetate have been given to normal patients without evidence of adrenal cortical atrophy.

and responded to intravenous administration of fluids or to transfusion of plasma or blood. There were no deaths from shock in either the treated or the control group.

Hematocrit determinations were made in a number of the cases before operation and at the time when shock developed or at the end of the operation.¹⁸ Hemoconcentration, as determined by the hematocrit, was manifest in about the same degree in both the treated and the control group. Moon¹⁹ and others have called attention to hemoconcentration as determined by the red cell count and the hematocrit as an early manifestation of shock. However, the value of this method for detecting developing shock during operations is limited, since hemorrhage causes irregularities; also, many of the operations were done with anesthesia induced by ether, and this agent increases the number of red cells in the circulation by contraction of the spleen. Hence these hemoconcentration studies are cited only as corroboratory evidence. It is thought that the number of thoracic operations and abdominoperineal resections of the rectum is large enough to prove conclusively that desoxycorticosterone in the doses used is of little value. Some doubt may be expressed whether enough intestinal and gastric operations have been followed to produce conclusive evidence. The incidence of shock associated with these procedures is normally low, and thus an unusually large series would be necessary to offer infallible proof.

Selye and his co-workers² and Weil and his associates^{16a} have recently published several reports of studies on traumatic shock in which cortical extracts, corticosterone and desoxycorticosterone were tested for their ability to prevent and relieve traumatic shock produced in laboratory animals by several methods. They found that desoxycorticosterone was of little value in this respect; however, cortical extract and pure corticosterone made animals more resistant to shocking procedures and tended to prevent the fall in plasma volume associated with these procedures. They suggested that desoxycorticosterone does not possess certain properties found in the extracts. Corticosterone is a steroid which is extracted from the adrenal cortex. Selye found this to be the most active steroid in producing resistance to shocking procedures. This product has not been synthesized, and the problem of obtaining it in large quantities has not been solved. Thus, if desoxycorticosterone is not effective in preventing operative shock, there is the possibility that a more active steroid, corticosterone, may prove of value.

18. Wintrobe hematocrit tubes and the Wintrobe technic were used.

19. Moon, V. H.: *Shock and Related Capillary Phenomena*, New York, Oxford University Press, 1938.

SUMMARY

Certain theoretic reasons and experimental evidence have been reviewed which form the basis for the postulate that adrenal cortical therapy may be of value in preventing shock associated with surgical procedures. Desoxycorticosterone acetate, a synthetic product having certain properties of adrenal cortical extract, was given to 72 patients undergoing extensive general surgical operations. The drug was given preoperatively. This product (in the dosage used) was found to be of little significant value in preventing shock, as evidenced by comparison of treated patients with controls.

SQUAMOUS CELL CARCINOMA ARISING IN A CHRONIC OSTEOMYELITIC SINUS TRACT WITH METASTASIS

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Carcinoma arising in a chronic osteomyelitic sinus tract has been reported sporadically for more than a hundred years and with somewhat greater frequency within the last decade. Nevertheless, the increasing incidence of chronic osteomyelitis that may be expected as a consequence of the war justifies directing attention to a complication that is by no means generally appreciated. This consideration and the fact that there are few reports of metastasis from carcinoma of an osteomyelitic sinus tract have prompted us to submit 2 cases and to review the literature.

The first case of this type of carcinoma appears to have been reported by Hawkins,¹ of London, England, in 1835, under the title "Cases of Warty Tumors in Cicatrices." Dittrich² in 1847 recorded the next case, in which the tibia was involved. Thigh amputation was performed, and the diagnosis of carcinoma was confirmed by Rokitsansky. Between 1851 and 1891 the following authors reported cases: Hannover,³ 1852; Cornil and Ranvier,⁴ 1866; Winiwarter,⁵ 1878; Esmarch,⁶ 1878; Nicoladoni,⁷ 1881; Fischer,⁸ 1881; Volkmann,⁹ 1889; Van Hook,¹⁰ 1890,

From the Department of Dermatology and the Laboratory Division, the Montefiore Hospital for Chronic Diseases, New York.

1. Hawkins, C.: Cases of Warty Tumors in Cicatrices, *Med.-Chir. Tr.* **19**:19, 1835.

2. Dittrich, H. F.: Ueber Epithelialwucherungen auf und in Knochen—sogenannte Epithelialkrebse, *Vrtljschr. f. d. prakt. Heilk.* **3**:363, 1847.

3. Hannover, A.: Das Epithelioma, Leipzig, L. Voss, 1852, pp. 12-150.

4. Cornil, V., and Ranvier, L.: Contributions a l'etude du développement histologique des tumeurs épithéliales (cancroïdes), *J. de l'anat. et physiol.* **3**:271, 1866.

5. von Winiwarter, A.: Beiträge zur Statistik der Carcinoms, Stuttgart, Ferdinand Enke, 1878; abstracted, *J. de méd., chir. et pharmacol.* **68**:424, 1879.

6. Esmarch, F.: Aphorismen über Krebs, *Arch. f. klin. Chir.* **22**:437, 1878.

7. Nicoladoni, C.: Epitheliombildung in Sequesterladen, *Arch. f. klin. Chir.* **26**:9, 1881.

8. Fischer, S.: Ueber die Ursachen der Krebskrankheit und ihre Heilbarkeit durch das Messer, *Deutsche Ztschr. f. Chir.* **14**:468, 1881.

(Footnotes continued on next page)

and Feigel,¹¹ 1891. In 1891 Borchers¹² compiled a list of 20 cases from the literature and added 5 cases of his own. Von Friedlander¹³ in 1894 reported 3 cases, and in the same year Devars¹⁴ reviewed 34 cases from the literature and described 5 additional cases. He stressed the tibia as the most common site for the development of carcinoma in chronic osteomyelitic sinuses. In 1897 Cone¹⁵ surveyed the literature and described 2 of his own cases. Between 1898 and 1904 additional cases were presented (Verdelet¹⁶; Cruchet¹⁷; Lanelongue¹⁸; Cargue¹⁹; Bauby²⁰; Guiot²¹; Sherrill²²). During the early twenties case reports were few (Mathieu and Khan²³; Hitzrot²⁴). In 1928 Vernengo²⁵ reported a case of this condition in a man of 24, and in 1929

9. Volkmann, R.: Ueber das primäre Krebs der Extremitäten, Samml. klin. Vortr., 1889, nos. 334-335 (Chir. no. 102), p. 3123.

10. Van Hook, W.: Carcinomas Arising in Inveterate Ulcers and in Ancient Sinuses, North Am. Practitioner 2:385, 1890.

11. Feigel, L.: Case of Primary Cancer of the Tibia, Przegl. lek. 30:457 and 470, 1891; cited by Benedict.²⁸

12. Borchers, F.: Ueber das Carcinom welches sich in alten Fistelgängen der Haut entwickelt, Inaug. Dissert., Göttingen, 1891.

13. von Friedlander, F. R.: Beitrag zur Kenntnis der Carcinomentwicklung in Sequesterhöhlen und Fisteln, Deutsche Ztschr. f. Chir. 38:473, 1894.

14. Devars, M.: De la dégénérescence cancéroïdale des anciens foyers ostéomyélitiques, Thesis, Lyon, no. 933, Lyon, A. Rey, 1894; abstracted, Lyon méd. 74:510, 1894.

15. Cone, S. M.: Squamous Epithelioma and Epithelial Hyperplasia in Sinuses and Bone Following Osteomyelitis, Bull. Johns Hopkins Hosp. 8:146, 1897.

16. Verdelet, L.: Epithélioma de la jambe développé sur d'anciens trajets d'ostéomyélite chronique du péroné, Bull. Soc. d'anat. et physiol. de Bordeaux 19:33, 1898.

17. Cruchet, M.: Epithélioma osseux secondaire à un trajet d'ostéomyélite ancienne, Bull. Soc. d'anat. et physiol. de Bordeaux 20:13, 1899.

18. Lanelongue, O.: Epithélioma osseux secondaire à un trajet d'ostéomyélite ancienne, J. de méd. de Bordeaux 29:162, 1899.

19. Cargue, G.: Dégénérescence épithéliomateuse des vieux foyers d'ostéomyélite, Thesis, Toulouse, no. 490, 1902; cited by Benedict.²⁸

20. Bauby, D.: Dégénérescence épithéliomateuse des vieux foyers d'ostéomyélite, Arch. prov. de chir. 11:96, 1902.

21. Guiot, J.: Dégénérescence cancéreuse de vieux foyers d'ostéomyélite, Thesis, Montpellier, no. 26, 1904; cited by Benedict.²⁸

22. Sherrill, J. G.: Osteomyelitis with Epithelioma of the Skin, Louisville Monthly J. M. & S. 10:303, 1903.

23. Mathieu, P., and Khan, T.: Epithélioma pavimenteux développé au contact d'un foyer ancien d'ostéomyélite chronique, Bull. et mém. Soc. anat. de Paris 90:210, 1920.

24. Hitzrot, J. M.: Epithelioma in Sinus of Old Osteomyelitis, Ann. Surg. 73:247, 1921.

25. Vernengo, M. J.: Epithelioma desarroblado en una fistula por osteomielitis crónica, Bol. y trab. de la Soc. de cir. de Buenos Aires 12:801, 1928.

Krey²⁶ mentioned a case reported by Mermet, of Paris, France. Young²⁷ described a case in 1930. Benedict²⁸ in 1931 reported 12 cases and reviewed the literature. Between 1931 and 1939 case reports were more frequent (Blanco²⁹; Collins³⁰; Hellner³¹; Henderson and Swart³²; Norinder³³; Placinteanu and Dobrescu³⁴). In 1939 Hobart and Miller³⁵ described 7 cases which, added to those of Benedict and Henderson, gave a total of 24 cases of carcinomatous degeneration in 5,196 cases of chronic osteomyelitis. Stewart, Obermayer and Woolhandler³⁶ in 1940 reported 1 case.

On the basis of reports in the literature the following observations may be made: The new growth (squamous cell carcinoma) occurs usually in men 40 to 60 years of age with a history of osteomyelitis and sinus tract formation of twenty to thirty years' duration, although a duration of fifty years is not uncommon. The most common sites are the tibia, the femur and the bones of the foot, in the order named. Carcinoma should be suspected if a cauliflower mass appears at the sinus opening (superficial type) or if a foul discharge occurs (deep type). Often there is no external evidence of carcinoma and only biopsy or roentgen examination of the bone or both will reveal its presence.

The favorable prognosis of this type of tumor has been stressed repeatedly by most authors, and the rarity of regional and visceral metastatic lesions has been emphasized. Borchers,¹² in his group of

26. Krey, W.: Ueber Fistelkarzinome an Hand eines Falles von Karzinom als Folge chronischer Fisteleiterung, *Deutsche Ztschr. f. Chir.* **215**:355, 1929.

27. Young, E. L., Jr.: Epidermoid Carcinoma of Femur: Chronic Osteomyelitis, Cabot Case 16342, *New England J. Med.* **203**:373, 1930.

28. Benedict, E. B.: Carcinoma in Osteomyelitis, *Surg., Gynec. & Obst.* **53**:1, 1931.

29. Blanco, P.: Squamous Cell Epithelioma Originating in Chronic Osteomyelitic Cavities: Two Cases, *Am. J. Cancer* **19**:373, 1933.

30. Collins, J. J.: Carcinoma in Chronic Osteomyelitis, *Am. J. Roentgenol.* **31**:787, 1934.

31. Hellner, H.: Carcinomatous Fistula Resulting from Chronic Osteomyelitis, *Fortschr. a. d. Geb. d. Röntgenstrahlen* **49**:109, 1934.

32. Henderson, M. S., and Swart, H. A.: Chronic Osteomyelitis Associated with Malignancy, *J. Bone & Joint Surg.* **18**:56, 1936.

33. Norinder, E.: Carcinomentwicklung bei chronischen osteomyelitischen bzw. osteitischen Prozessen, *Acta orthop. Scandinav.* **8**:381, 1937.

34. Placinteanu, G., and Dobrescu, D.: Fistelkarzinom auf den Boden chronischer Osteomyelitis, *Zentralbl. f. Chir.* **64**:1447, 1937.

35. Hobart, M. H., and Miller, O. S.: Cutaneous Carcinoma and Acoustic Neuritis, *Am. J. Surg.* **45**:53, 1939; Osteomyelitis at Cook County Hospital, *J. A. M. A.* **107**:1118 (Oct. 3) 1936.

36. Stewart, C. D.; Obermayer, N. D., and Woolhandler, H.: Cutaneous Metastatic Carcinoma Originating from Osteomyelitic Cavities, *Arch. Dermat. & Syph.* **41**:545 (May) 1940.

25 cases, noted that metastases were rare and that there were no metastases beyond the regional lymph nodes. However, his diagnosis of lymph node involvement was based on enlargement of lymph nodes and not on biopsy. In Devars' ¹⁴ 39 cases there were no metastases. Cone, ¹⁵ in his analysis of the literature, emphasized the infrequent metastatic involvement of lymph nodes or other organs. He stated also that the lymphadenopathy may be inflammatory, as the nodes often become smaller after amputation. He suggested, therefore, that in the reported cases of involvement of lymph nodes with metastatic carcinoma, especially those of Borchers, ¹² the condition may have been inflammatory. Bauby ²⁰ reaffirmed the point that visceral metastasis is rare and that involvement of lymph nodes is probably inflammatory rather than metastatic. Benedict ²⁸ stated that this type of carcinoma is slow growing and that the prognosis is favorable. In none of his cases did metastases occur. In the most recent discussion (Stewart, Obermayer and Woolliandler ³⁰) the authors reemphasized the fact that metastases seldom occur and in any event rarely go beyond the regional lymph nodes. As a further confirmation of the relatively benign course of these lesions, most authors (Volkman ⁹; Cone ¹⁵; Benedict ²⁸; Henderson and Swart ³²) have maintained that amputation is curative in most instances.

As far as we can ascertain, only 7 cases of metastases from carcinoma arising in chronic osteomyelitic sinus tracts have been reported in the literature. Volkman ⁹ reported 3 such cases. He gathered the first 2 from the literature and added a third of his own. Case 1 was that of Bartens, in which the tibia was the site of a sinus tract. An amputation was performed, but metastases developed and the patient died. Autopsy revealed carcinoma in the inguinal and mesenteric lymph nodes, liver and costal pleura. In case 2, reported by von Bruns, the patient also came to autopsy, and metastatic lesions were found in the liver, breast, kidneys, ribs and adjacent lymph nodes. In case 3 (Volkman ⁹) there was a carcinoma arising in an osteomyelitic sinus of the shoulder, with metastases to regional lymph nodes, namely, the axillary and the supraclavicular. Disarticulation of the humerus was performed, but the patient committed suicide four months later. Autopsy was not recorded. Krey ²⁶ mentioned a case, reported by Mermet, in which carcinoma occurred in a chronic osteomyelitic sinus of the tibia and metastases appeared in the contiguous femur, with fracture. However, no details of this case were given. Bauby ²⁰ reported the case of a 62 year old man with an osteomyelitic sinus tract of the tibia of fifty years' duration. This man died, and autopsy revealed a squamous cell carcinoma involving the lymph nodes and the right lobe of the liver. Bauby expressed the belief that this arose from the chronic sinus tract. Hellner ³¹ added a

case in which autopsy disclosed general lymph node, pleural and pulmonary metastases. Stewart, Obermayer and Woolhandler³⁶ reported a case of carcinomatous degeneration of the epithelial lining of a chronic osteomyelitic cavity with cutaneous metastatic lesions of squamous cell carcinoma.

Of the aforementioned 7 cases, 4 (those of Bartens and von Bruns, both cited by Volkmann,⁹ that of Bauby²⁰ and that of Hellner³¹) are definite cases of visceral metastases proved by autopsy. In Volkmann's own case there was merely enlargement of regional lymph nodes which may have been inflammatory; neither biopsy nor autopsy was mentioned. In Mermet's case²⁶ the tibia was the original site, and a lesion developed in the femur which Krey concluded was metastatic but which may have been due to direct extension. In the most recent case, that of Stewart and his associates,³⁶ there were no visceral metastases, but cutaneous metastases developed in the arm after amputation of the thumb for osteomyelitis. In summary, there are only 4 cases in which metastatic lesions definitely occurred in the viscera and only 1 in which metastases to the skin were observed. It is because of this rarity that the following 2 cases are reported.

REPORT OF CASES

CASE 1.—A 76 year old white man was admitted to the surgical service of the Montefiore Hospital. He was convalescing from a high thigh amputation of the left leg, performed eight days previously at another hospital. His history revealed that twenty-five years previously he had fractured his left patella. This was repaired, but a persistent postoperative sinus remained in the region of the upper part of the left tibia. Ten days prior to admission to the Montefiore Hospital the patient suffered a fracture of the left tibia in the region of the old sinus tract following a fall. At another hospital the condition was diagnosed as chronic osteomyelitis of the tibia with squamous cell carcinoma about a chronic sinus tract, complicated by a pathologic fracture. High thigh amputation was performed, and eight days later the patient was transferred to the Montefiore Hospital. Physical examination revealed him to be fairly well developed, with no evidence of loss of weight. Bilateral chronic fibroid apical tuberculosis was found. A roentgenogram confirmed this and revealed also thin-walled cavities on the left and a thickened pleura on the right. A left midhigh guillotine amputation with a granulating base was present. A roentgenogram of the stump revealed atrophy of the remainder of the shaft of the femur. The wound healed nicely, but five months later an indurated nodule, appearing in the stump, began to suppurate. This was followed by progressive enlargement of the left inguinal lymph nodes, which became indurated. The mass in the stump grew, and a specimen was taken for microscopic examination. In the report it was described as follows: "Squamous cell carcinoma with pearl formation and a moderate degree of pleomorphism is present. In the depths of the corium, extending downward, are numerous irregular confluent islands of tumor cells in a mosaic pattern resembling cells of surface epithelium." A roentgenogram taken at this time revealed "atrophy of the remaining portion of the left femur and bony fragments below and mesial to the stump; the lower one is probably a sequestrum, while the mesial ones are

probably due to new bone production." During his stay in the hospital the patient had mild normocytic anemia and leukocytosis, with a leukocyte count of 12,400 per cubic millimeter of blood. The Wassermann reaction was negative. The value for

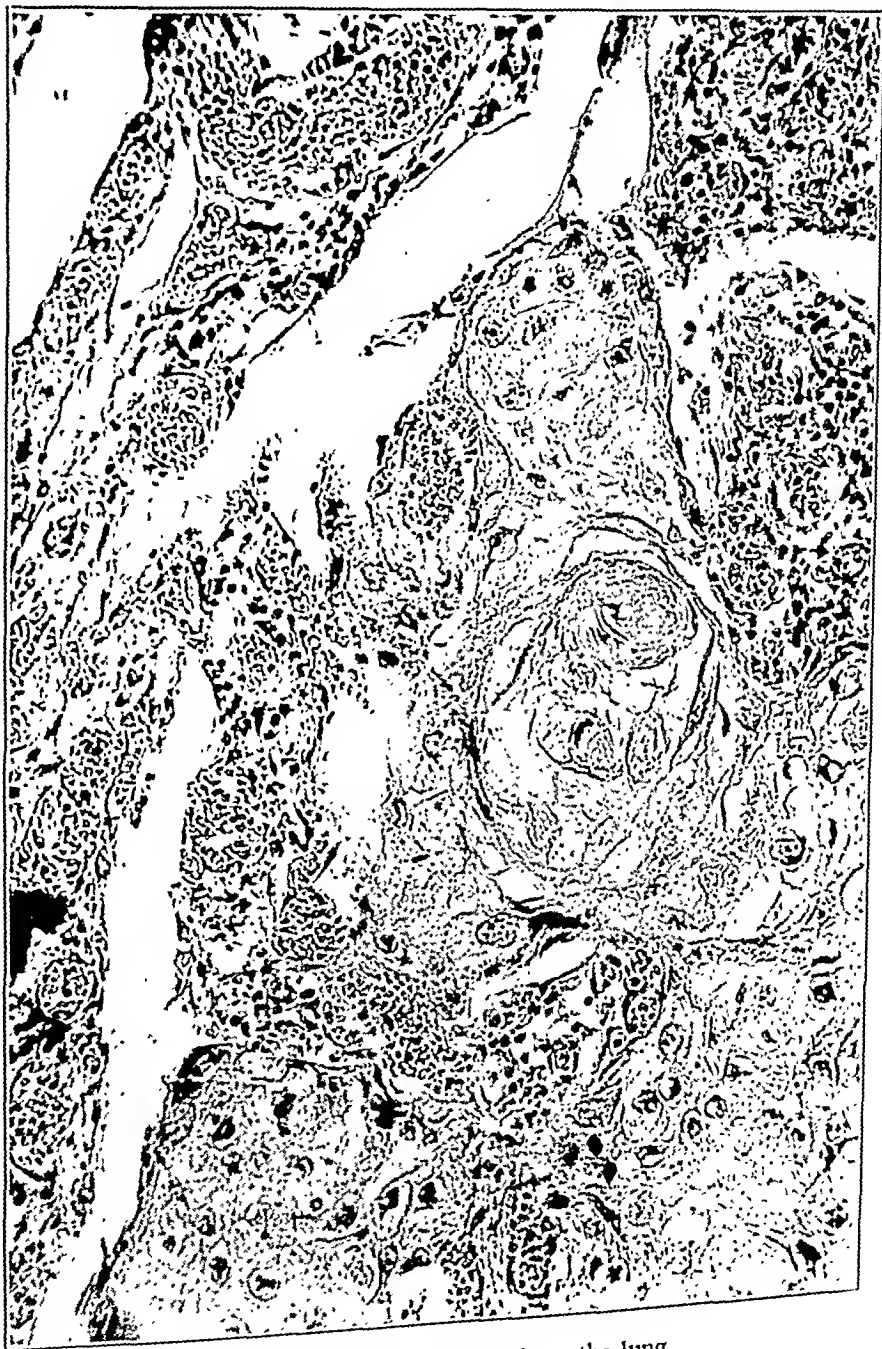


Fig. 1 (case 1).—Metastasis to the lung.

blood sugar was 149 mg. per hundred cubic centimeters. Examination of the urine gave negative results. The patient became progressively weaker, and the mass fungated rapidly. Six weeks after the first appearance of the nodule the patient died.

Autopsy.—The body was somewhat emaciated. There was a well healed amputation stump at the upper third of the left thigh. No enlargement of the lymph nodes was present. On the anterior aspect of the stump of the left lower extremity

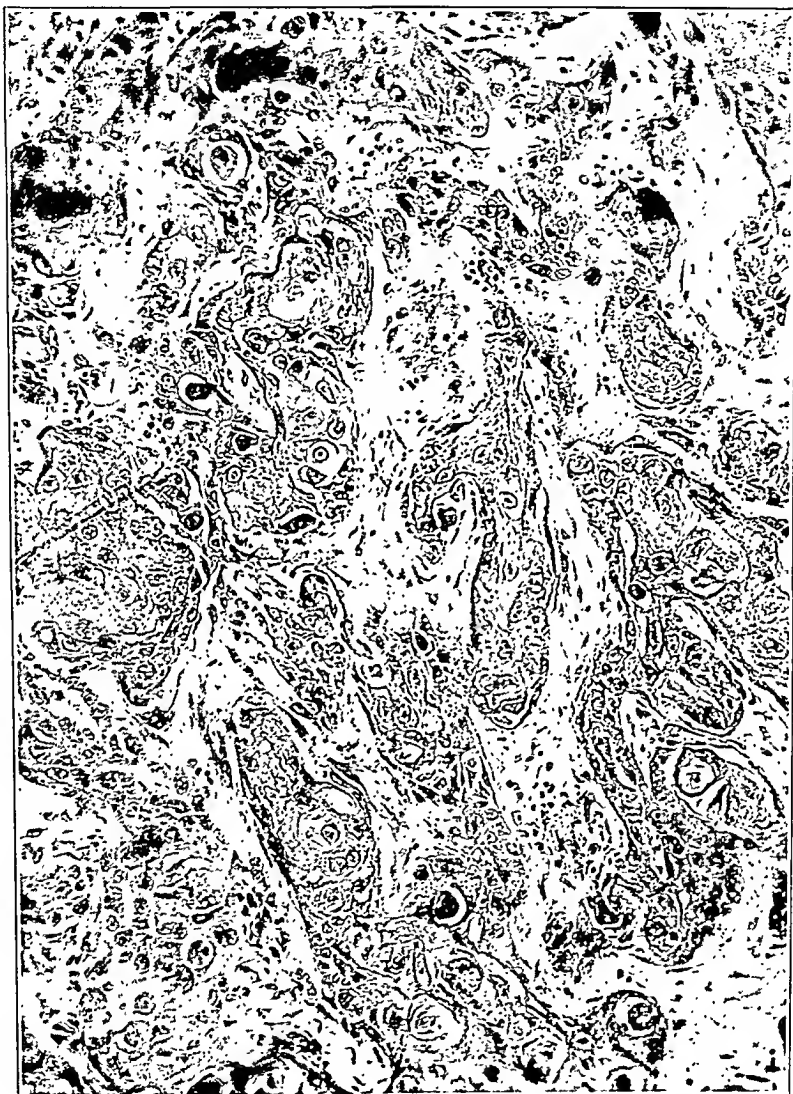


Fig. 2 (case 1).—Primary growth.

was a deep necrotic ulcer measuring about 4 by 3 by 2 inches (10 by 7 by 5 cm.), with thickened, everted edges. The edges were about $\frac{1}{4}$ to $\frac{1}{2}$ inch (0.6 to 1.2 cm.) in diameter and protruded about the same distance above the level of the skin. They were made up of firm white tissue. The outer portion was covered by the

skin, and the inner portion made up the sides of the ulcer. The sides and base of this ulcer were composed of soft, black-red tissue which extended down to the femur. In some places the base was infiltrated with the same firm, white tissue seen in the edges. A sinus tract to the bone was not found. The heart showed some hypertrophy of the left ventricle, a healed infarct of the posterior wall of the left ventricle, including part of the interventricular septum, and marked sclerosis and narrowing of the coronary arteries. There were fibrosis, anthracosis and calcification at the apexes of both lungs, with some bronchiectasis in the upper lobe of the left lung. At the base of the right lung was a small, firm white nodule. There were arteriosclerosis and arteriolosclerosis of the kidneys, which were smaller than normal and had a finely and coarsely granular surface. The prostate was enlarged in its median lobe. The rest of the autopsy revealed no abnormalities.

Microscopic Appearance: The lower lobe of the right lung showed a large nodule of tumor compressing the surrounding lung tissue. The tumor was made up of darkly staining anaplastic polygonal cells. These cells were growing in whorls, masses and strands. There were many pearls (fig. 1). The skin at the stump showed a small area in which there was an irregular downgrowth of hyperplastic interpapillary pegs. The basement membrane was intact, and mitotic figures were scarce. At one edge this epithelium ended abruptly, and the remainder of the section was replaced by cords, anastomosing strands and a concentric arrangement of anaplastic cells which took a deep basic stain. Mitotic figures were abundant. Pearl formation was most common near the surface of the ulcerated area (fig. 2). The tumor from the base of the ulcer was as previously described. Microscopic examination of the other organs revealed no other significant abnormalities pertinent to the subject.

CASE 2.—A 62 year old white woman was admitted to the surgical service of the Montefiore Hospital, complaining of pain and swelling in the left knee of two months' duration. At the age of 11 years she had fallen and injured her left knee. After this there was slight limitation in motion, which persisted. At the age of 39 the patient noticed pain in the left knee and was admitted to a hospital, where a diagnosis of tuberculosis with ankylosis of the left knee joint was made. Subsequently, excision and fusion of this joint were performed. The patient improved and the pain disappeared, but a persistent draining sinus remained at the operative site. In January 1933, when the patient was 62 years of age, the pain recurred in the left knee and a reddened, cystic mass appeared at the site of the old sinus tract. The patient was readmitted to the same hospital, where a portion of the outer condyle of the femur was removed and microscopic examination disclosed squamous cell carcinoma arising at the margin of an old osteomyelitic sinus. No evidence of tuberculosis was found. After operation the sinus continued to drain. In August 1933 the patient fell on her left side and was unable to rise. Pain and swelling from the knee to the hip appeared soon afterward, and two months later the patient was admitted to the Montefiore Hospital. Physical examination revealed a swelling of the left thigh from the knee to the hip and a sinus of the left knee with red granulating edges and a purulent exudate. The lower half of the thigh had a brawny consistency and was painful to touch. A biopsy specimen was taken at the site of the sinus, and microscopic examination revealed chronic granulation tissue and atypical epithelial proliferation with early malignant changes. A roentgenogram of the left knee showed an extensive des-

tructive process of the lower end of the shaft of the femur, with invasion of the soft parts anteriorly and destruction of the tuberosity of the tibia and of the upper end of the shaft of the fibula. There was complete disorganization of the left knee joint. The picture was that of a neoplasm of bone. A roentgenogram of the pelvis demonstrated areas of osseous absorption in the body of the left pubic bone and in the descending ramus of the right pubic bone. Areas of osseous sclerosis were present in the right ischium. The roentgen impression was "metastatic neoplasm of the bones of the pelvis" (fig. 3). In view of this, operation seemed contraindicated. The patient gradually became weaker. She died eight months after admission.

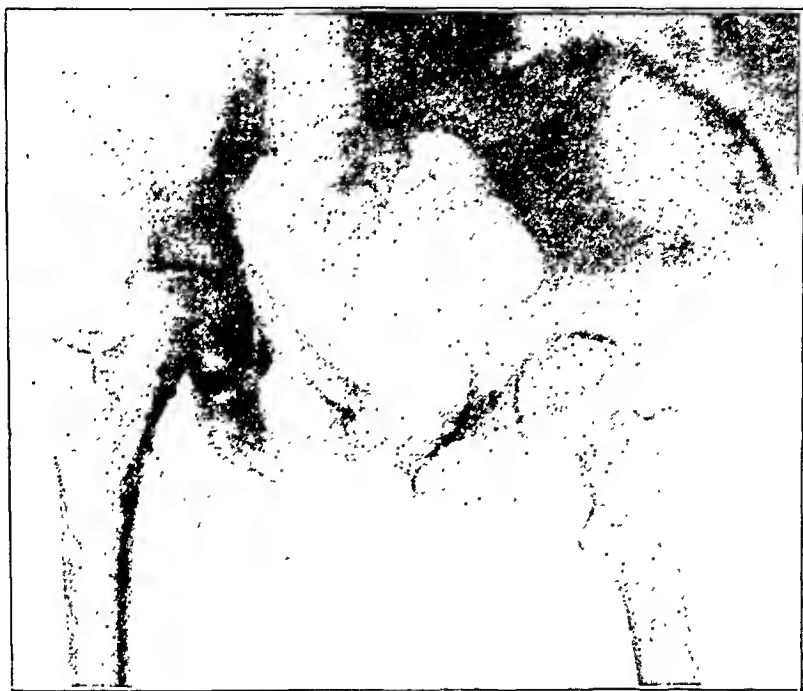


Fig. 3 (case 2).—Metastasis to the pelvis.

Autopsy.—The body was fairly well developed and showed evidence of slight loss of weight. There was marked pallor of the skin and the visible mucous membranes. The left leg was 20 cm. shorter than the right, and in the region of the left knee joint there were two defects in the skin, each approximately 10 cm. in diameter. These lesions were surrounded by a small zone of scar tissue, next to which was a smaller zone of hemorrhage into the skin, covered by a blood crust. A purulent, fetid discharge was present. The lungs, heart and kidneys were essentially normal. The liver was somewhat fatty. The remainder of the autopsy revealed no significant abnormalities pertinent to our subject.

Microscopic Appearance: The skin in the region of the sinus of the left knee showed hyperplasia of the epithelium with irregular downgrowth of the interpapillary pegs. The cells were polygonal, with large nuclei and fairly large nucleoli.

Mitoses were rare. At one edge pearl formation and groups of anaplastic cells were seen. In the dermis and subcutaneous tissue there was round cell infiltration (fig. 4). The rest of the microscopic examination showed an essentially normal picture. A section of the pelvic bone was not obtained.



Fig. 4 (case 2).—Primary tumor.

COMMENT

Our first case, in which metastatic lesions occurred in the lung, is, as far as we know, the second one of its kind reported. Hellner²¹ reported the first example. In our case it is interesting to note that

in spite of amputation a local recurrence developed in the stump. In our second case there was roentgen evidence of metastasis to the pelvic bones. Metastasis to bone is comparatively rare, the only previous reports being those of Volkmann⁹ and Krey.²⁶

The origin of this type of carcinoma has been discussed by many authors since it was first described. The early authors emphasized the chronic irritation of the skin about the sinus outlet by continuous drainage of pus and, on the basis of Cohnheim's theory, considered this irritation the cause of the malignant change. This was thought to account for the superficial type of carcinoma. The deep type of carcinoma, i. e., that in the depth of the sinus tract, was not so readily explained. Most of these early authors considered the latter a downgrowth of a malignant tumor originating in the skin at the sinus opening. Rokitansky,³⁷ in fact, in 1847 stated that this had occurred in Dittrich's case. Devars,¹⁴ however, spoke of a superficial carcinoma appearing as an ulceration or a cauliflower mass in the skin about the sinus tract and of a deep carcinoma arising in the depth of the sinus and manifesting its presence by a foul discharge.

In recent years the work of Brunschwig³⁸ and Milgram³⁹ has clarified the conception of the origin of the deep type of carcinoma. Milgram called attention to the fact that chronic osteomyelitic sinuses and cavities tend to become lined by squamous epithelium growing down from the surface of the skin. In the case he reported malignant degeneration was not evident. Brunschwig³⁸ reported 3 cases of chronic osteomyelitis with a long-standing draining sinus lined with epithelium in which pearl formation was seen. In his cases malignant degeneration was not observed, but he emphasized that the chronic inflammatory process in such a sinus cavity affords a stimulus for neoplastic changes in epithelial cells. This was not a new idea, for in 1894 Wassermann and Hallé,⁴⁰ reporting 12 cases of infection of the urethra with and without stricture and with fistulous tract formation, had mentioned complete epithelialization of the fistulous tract from the urethral mucosa. In some of the tracts the proliferation of the epithelial lining was so great as to make one think of epithelial new growths. Kaufman⁴¹ mentioned that a fistula from bone that has become epithelized may undergo malignant change.

37. Rokitansky, cited by Dittrich.²

38. Brunschwig, A.: Epithelialization of Bone Cavities and Calcification of Fibrous Marrow in Chronic Pyogenic Osteomyelitis, *Surg., Gynec. & Obst.* **52**:759, 1931.

39. Milgram, J.: Epithelialization of Cancellous Bone in Osteomyelitis, *J. Bone & Joint Surg.* **13**:319, 1931.

40. Wassermann, N., and Hallé, N.: Urétrite chronique et rétrécissements, *Ann. d. mal. d. org. génito-urin.* **12**:241 and 321, 1894.

41. Kaufman, E.: *Lehrbuch der speziellen pathologischen Anatomie*, Berlin, Walter de Gruyter, 1922, vol. 2, p. 1711.

Concerning the rarity of metastases two possible explanations may be offered: 1. The low grade malignancy of the new growth, which has been emphasized by a number of authors on the basis of biopsies. 2. The possibility that many of the tumors which have been reported as malignant may have been pseudoepitheliomatous hyperplasia, a term applied by White and Weidman⁴² to a benign overgrowth of epithelium. These authors, describing the histologic changes in 8 cases of chronic cutaneous ulcer, divided their lesions into 3 groups, all clinically benign yet histologically resembling squamous cell carcinoma (especially groups 2 and 3). They stated that "it may be impossible to distinguish squamous cell carcinoma histologically from these non-malignant hyperplasias" and emphasized the fact "that numerous cases diagnosed in the past as beginning carcinoma at the margins of ulcers, have been only exaggerated regenerative hyperplasia." It is quite possible, therefore, that some of the cases in which cure of the malignant tumor was attributed to amputation may have been instances of pseudoepitheliomatous hyperplasia rather than of actual malignant tumor.

SUMMARY

Two cases of squamous cell carcinoma arising in a chronic osteomyelitic sinus with metastases are reported. Necropsy was performed in both instances. In the first, metastases were found in the lung. In the second, diagnosis of metastases in the pelvic bones was based on roentgen evidence, since a specimen of the bones was not obtained at necropsy.

The rarity of metastases from squamous cell overgrowth, as revealed in a review of the literature, may be explained by the low grade of malignancy and by the possibility that some of the reported cases may have been instances of pseudoepitheliomatous hyperplasia rather than of true malignant tumor.

42. White, C., and Weidman, F. D.: Pseudo-Epitheliomatous Hyperplasia at the Margins of Cutaneous Ulcers, *J. A. M. A.* 88:1959 (June 18) 1927.

PANCREATIC FISTULA

CLINICAL AND EXPERIMENTAL OBSERVATIONS

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AND

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ST. LOUIS

Although Wirsung¹ as early as 1645 had discovered the pancreatic duct and described the fluid which flows through it and DeGraaf² in 1664 had collected some of this fluid, using a wild duck's quill for a cannula, present knowledge of the physiology of the external function of the pancreas came largely as a result of the work of four investigators in the late part of the nineteenth and the early part of the twentieth century, namely, Bernard,³ Pavlov⁴ and Bayliss and Starling.⁵ Bernard in 1856 showed that pancreatic juice is essential to digestion. Pavlov in 1902 demonstrated the existence of pancreatic enzymes, and in the same year Bayliss and Starling investigated the factors concerned in the secretory stimulus of the pancreas and assigned the important role to a humoral factor, which they named secretin.

McClure⁶ has enumerated as follows the important physiologic facts, which are now firmly established: 1. Stimulation of the external secretion of the pancreas is of humoral origin, although the exact mechanism remains undetermined. 2. The ingestion of food is followed by secretion of pancreatic juice. 3. The external secretion of the pancreas plays an essential role in digestion.

From the Department of Surgery, St. Louis University School of Medicine.

Read at the Fiftieth Annual Meeting of the Western Surgical Association, Topeka, Kan., Dec. 5, 1940.

1. Wirsung, cited by Garrison, F. H.: *History of Medicine*, ed. 3, Philadelphia, W. B. Saunders Company, 1921.

2. DeGraaf, R., cited by Garrison, F. H.: *History of Medicine*, ed. 3, Philadelphia, W. B. Saunders Company, 1921, p. 263.

3. Bernard, C.: *Mémoire sur le pancréas et sur le rôle du suc pancréatique dans les phénomènes digestifs, particulièrement dans la digestion des matières grasses neutres*, Paris, J. B. Bailliére, 1856.

4. Pavlov, I. P.: *The Work of the Digestive Glands*, translated by W. H. Thompson, ed. 2, London, Charles Griffin & Co., 1910, p. 266.

5. Bayliss, W. M., and Starling, E. H.: *The Mechanism of Pancreatic Secretion*, *J. Physiol.* 28:325-353, 1902.

6. McClure, C. W.: *Observations on the Physiology and Pathologic Physiology of External Pancreatic Functions*, *Rev. Gastroenterol.* 3:1-26, 1936.

METHODS OF OBTAINING PANCREATIC JUICE

A great variety of ingenious methods have been devised for collecting pancreatic juice from an experimental animal. Objections of one kind or another, such as duct strictures, infections, interference with nerve and blood supply, pancreatic atrophy and autodigestion of the adjacent parietal walls can be made to most of these methods. The important thing is to distinguish between a partial and a total fistula. In earlier experiments, in which the fistulas were subtotal or in which the animal was allowed to lick its secretions, little harm resulted; however if the fistula is truly total, death follows rapidly, as Elman and one of us (McCaughan)⁷ demonstrated in 1927.

Pancreatic juice for study may be obtained from the human being by two methods: (1) by intubation with a Rehfuess tube and (2) by fistula. By the former method one obtains a juice which is mixed with other intestinal secretions; the latter requires a patient whose pancreas has been injured. Injury of the pancreas is rare, which is fortunate for human beings in general if not for clinical physiologists bent on studying the factors in external pancreatic secretion.

TOTAL VOLUME OF PANCREATIC JUICE

The total volume of pancreatic juice obtained in experiments with total fistula in dogs depends on several factors but has ranged in our experiments from a few cubic centimeters to as much as 625 cc. per diem. In human beings with pancreatic fistulas the maximum volume was reported by Snyder and Lium,⁸ who obtained 1,186 cc. of pure pancreatic juice per twenty-four hour period direct from a catheter in the duct of Wirsung.⁹

PHYSICAL AND CHEMICAL PROPERTIES OF PANCREATIC JUICE

Pure pancreatic juice is a clear, slightly opalescent alkaline fluid, containing 98.45 to 98.86 per cent of water, 1.13 to 1.86 per cent of total solids, 0.075 to 0.098 Gm. of nitrogen, 0.099 to 0.174 Gm. of coagulable protein, 0.410 to 0.475 Gm. of globulin, 0.086 to 0.152 Gm. of albumin and 0.580 to 0.950 Gm. of ash. The specific gravity varies from 1.005 to 1.014, and the p_H ranges from 8.2 to 8.5. Three ferments, lipase, amylase and inactive trypsin, are present.

7. Elman, R., and McCaughan, J. M.: On the Collection of the Entire External Secretion of the Pancreas Under Sterile Conditions and the Fatal Effect of Total Loss of Pancreatic Juice, *J. Exper. Med.* **45**:561-570, 1927.

8. Snyder, W. H., and Lium, R.: Pancreatic Fistula, *Surg., Gynec. & Obst.* **62**:57-64, 1936.

9. Recently (at the fiftieth annual meeting of the Western Surgical Association) V. C. Hunt reported a considerably larger total per diem output in a case of his own; the data are as yet unpublished.

SECRETION OF PANCREATIC JUICE

The popular description of the process, with some reservations based on recent studies,⁶ is as follows: The secreting mechanism depends largely on the stimulus from the acid chyme as it enters the first part of the duodenum. Immediately a certain amount of secretin is carried by the blood to the acinar cells of the pancreas and excites there the secretion of a strongly alkaline pancreatic juice. As soon as enough juice is present to neutralize the acid chyme, secretin formation and hence further pancreatic secretion stop. As long as the duodenal contents are acid the pylorus remains closed; therefore, as soon as these contents are neutralized the pylorus relaxes and allows more acid chyme to enter. Thus the formation of secretin proceeds afresh, and the whole chain goes on until the stomach is empty.

Experimental and clinical observations were made on human pancreatic secretion in the following cases.

REPORT OF CASES

CASE 1.—A girl 10 years of age was admitted to the St. Louis County Hospital after an injury to the abdomen sustained while coasting on a sled. She complained of constant pain in the right upper quadrant, with paroxysmal intensification at frequent intervals and radiation to the right flank and lumbar region. There were vomiting and a temperature of 100 F.; the pulse rate was 120 and the respiratory rate 26 per minute. The blood pressure was 94 systolic and 70 diastolic. Examination of the abdomen revealed generalized tenderness, slight distention and board-like rigidity, particularly in the right upper quadrant. There was no dulness, either fixed or shifting, in the flank. Urinalysis revealed no abnormality. The leukocyte count was 25,000 per cubic millimeter; the value for hemoglobin, 72 per cent, and the erythrocyte count, 4,100,000 per cubic millimeter. The differential count was essentially normal. The value for blood sugar was 100 mg. per hundred cubic centimeters and that for blood diastase 680 units. The girl was given parenteral fluids, and surgical exploration was done seventy-two hours after the injury. At operation the abdomen contained a small amount of bloody fluid, and there were lacerations of the right lobe of the liver. The omentum was adherent and drawn together in the region of the pancreas. The lesser sac was drained.

The child made an uneventful recovery except for profuse drainage from the wound of a clear watery fluid which was identified as pancreatic juice. The skin adjacent to the fistula became excoriated and was protected with a paste made from aluminum powder, zinc oxide and olive oil; also, a solution of acidified beef broth was applied, and continuous suction was made by means of a catheter in the fistulous tract connected to a Wangenstein apparatus. A diet of 150 Gm. of fat and 100 Gm. of protein was given by tube, together with calcium gluconate and all the pancreatic juice which could be recovered. Later, 25 Gm. of carbohydrate was added and the diet was administered by mouth. The fistula gradually closed, and the patient was discharged from the hospital six months after the date of injury.

CASE 2.—A single white woman 50 years of age was admitted to St. Mary's Hospital on March 28, 1935, complaining of attacks of loss of consciousness with generalized convulsions since Jan. 1, 1934. There were attacks of both petit mal

and grand mal. Sugar tolerance tests gave low readings, and a presumptive diagnosis of hyperinsulinism was made. Surgical exploration was done on May 22, 1935, and a portion of the pancreas was extirpated. The pathologist reported hypertrophy and hyperplasia of the islet tissue. The postoperative course was uneventful except for the development of a pancreatic fistula. The drainage was estimated at 300 to 400 cc. daily. The Wohlgemuth regimen, namely, a diet high in carbohydrate and alkaline foods with large doses of sodium bicarbonate and belladonna, was instituted. The drainage diminished considerably, and the patient returned to her home. She came back five days later, complaining of nausea, vomiting and severe pain in the left upper quadrant, the left flank and the back. She had a temperature of 100.8 F. Fluid was aspirated and on microscopic examination was found to contain large numbers of pus cells and organisms identified as *Staphylococcus albus haemolyticus*. An attempt was made to inhibit pancreatic drainage with high voltage roentgen ray treatments, but this was without appreciable effect. On July 28 20 cc. of iodochlorol (a radiopaque iodine and chlorine addition product of peanut oil) was injected into the fistula, and roentgenograms were taken. Two large cysts, one superimposed on the other, connected by a tortuous tract with the cutaneous opening, were discovered. The cysts were drained surgically, and the patient made a satisfactory recovery. At the time of her discharge from the hospital, on September 17, the drainage had ceased and the wound was entirely healed.

CASE 3.—A white man 23 years of age was admitted to the St. Louis County Hospital on Aug. 11, 1940, after an automobile collision during which he was struck on the abdomen by the cowl in front of the rumble seat, in which he was riding. On admission he was in shock and complained of agonizing generalized abdominal pain. Roentgen examination showed no free air beneath the diaphragm. After treatment had been given for shock, an exploratory laparotomy was performed. There was some free blood in the lesser peritoneal cavity, which apparently had come from a complete transverse severance of the pancreas in the midportion of its body. The hemorrhage was controlled by suturing, and the severed end of the distal portion was closed with mattress sutures; it was hoped thereby to occlude the duct of Wirsung, which could not be identified because of blood clot and contused parenchymal tissue. A drain was brought out through the gastrocolic ligament.

The patient remained in a critical condition for several days and then began to improve. Repeated blood transfusions were given. Drainage of pancreatic juice appeared almost immediately after operation, and the value for blood diastase on the first day after the operation was 1,500 units. Unfortunately there developed a pneumonic consolidation of the left lower part of the chest, and, in addition, on August 21 the wound began to separate, requiring secondary closure. Shortly after this operation, 1,100 cc. of sterile, turbid, straw-colored fluid was aspirated from the left pleural cavity. The patient died on August 23. At postmortem examination a necrotic abscess was found in the middle third of the pancreas. The head and the tail of the pancreas were normal. There were multiple areas of fat necrosis adjacent to the omentum, mesenterics and perirenal fat. There were subcapsular hemorrhages in the liver and adrenals, and serofibrinous peritonitis was observed. Bronchopneumonia was present in the lower lobe of the left lung, and there was serosanguinofibrinous pleurisy. Cultures of the blood and of material from the pleural space showed *Staph. aureus haemolyticus* and pneumococci.

CASE 4.—The patient, a white man 20 years of age, entered the Firmin Desloge Hospital Sept. 27, 1940, complaining of severe pain in the epigastrium and vomiting which had begun three hours earlier. The temperature was 98.6 F., the pulse rate 78 and the respiratory rate 20. Examination of the abdomen revealed exquisite tenderness in the epigastrium but no muscle spasm and no masses. On laboratory examination the leukocyte count was 32,000 per cubic millimeter, with 20 per cent stab forms, 64 per cent segmented forms and 16 per cent lymphocytes. Urinalysis showed albumin (graded 2 plus) and sugar (graded 4 plus); the specific gravity of the urine was 1.030. The principal laboratory finding was a value for blood diastase of 740 units. A diagnosis of acute pancreatitis was made, and on September 29 an exploratory operation was done and the diagnosis confirmed. A cholecystostomy was done; drains were inserted to the foramen of Winslow and through the gastrocolic omentum down to the necrotic area in the pancreas. The patient's course at first after operation was somewhat stormy, but later he improved gradually. Drainage of pancreatic juice was noted almost immediately, and at the end of three weeks a large piece of necrotic pancreas (1 by 3½ inches [2.5 by 9 cm.]) was discharged from the wound. The patient continued to improve and is at present permitting us to carry on a number of other physiologic studies. These data, however, are not complete and cannot be presented at this time.

CASE 5.¹⁰—A man aged 49 years was admitted to the Firmin Desloge Hospital on Jan. 15, 1936. He had been operated on elsewhere, and a pancreatic fistula had followed a Billroth II gastric resection. It had been draining for more than nine months at the time of admission, and during much of this time Wohlegemuth's antidiabetic regimen had been carried out for the purpose of encouraging spontaneous closure of the fistula. On admission the fistula was seen to be situated about 4 cm. below the xyphoid, in the median line. It barely admitted the tip of a small probe and emitted a clear watery fluid in profusion. The surrounding skin was only slightly excoriated. The fluid was collected and identified as pancreatic juice. The general physical and laboratory examinations gave essentially negative results. Roentgen examination showed that the stomach had been resected at its distal third and a gastroenterostomy made 5 cm. proximal to the blind end. The barium sulfate passed freely through the stoma. On February 1 the fistula was implanted into the anterior wall of the stomach. The patient made a satisfactory recovery and was discharged from the hospital March 15.

Experimental Procedure.—Prior to the operation, physiologic studies were made and the response to various excitatory and inhibitory drugs and foodstuffs was recorded. A small glass funnel was first applied to the skin about the opening of the fistula and was held there with adhesive tape. The patient was placed in the prone position on two tables set end to end in such a manner that the secretion could drop between the tables and onto the recording and collecting apparatus. At least two hours was permitted to elapse after a meal before the beginning of the experiment. Samples of the secretion were collected at regular intervals, usually every fifteen minutes. The total alkali in each specimen was titrated with tenth-normal hydrochloric acid, and the rate of flow was measured before and after each experiment.

10. Previously reported (McCaughan, J. M., and Sinner, B. L.: Pancreatic Fistula: Medical and Surgical Management, Arch. Surg. 35:449-460 [Sept.] 1937. McCaughan, J. M.; Sinner, B. L., and Sullivan, C. J.: External Secretory Function of the Human Pancreas: Physiologic Observations, Arch. Int. Med. 61:739-751 [May] 1938).

Results.—The amount of secretion was found to be least during fasting and greatest after meals. The average loss per diem was estimated at 600 cc. A rise in secretory rate followed the administration of secretin, a mixed meal, water, mecholyl chloride (acetylbetamethylcholine hydrochloride) and physostigmine salicylate. A fall in the secretory rate occurred after administration of sodium bicarbonate, bile salts, magnesium sulfate, atropine sulfate, epinephrine hydrochloride and histamine. The value for total base was elevated after the administration of secretin, sodium bicarbonate and coffee and was depressed after the administration of mixed meal, beef broth, dextrose, bile salts, physostigmine, epinephrine and histamine. There was no significant change in total base after administration of hydrochloric acid, peptone and magnesium sulfate.

CASE 6.—A white man aged 52 years was admitted to the Firmin Desloge Hospital Sept. 14, 1939, complaining of pain in the region of the gallbladder. He also complained of severe itching and was deeply jaundiced. The stools were clay colored and the urine dark. He had lost 10 pounds (4.5 Kg.) in weight since the onset of the illness, seven months previously. On examination the edge of the liver could be felt 4 cm. below the right costal margin, and there was tenderness, most marked in the epigastrium. On laboratory examination the erythrocytes numbered 4,209,000 and the leukocytes 8,450 per cubic millimeter of blood; the value for hemoglobin was 14.9 Gm. The differential count was normal. The bleeding time and the clotting time were two and one-half and four minutes respectively. The van den Bergh reaction was direct immediate positive and varied from 3.6 to 6.2 mg. per hundred cubic centimeters on different days. The icterus index was 75. The urine contained bilirubin but was otherwise normal. The prothrombin time was eighty seconds; the value for cholesterol was 342 mg. per hundred cubic centimeters, and that for blood diastase, 380 units. Gastrointestinal roentgen examination showed an irregularity of the duodenal bulb, which was thought to be due to cicatricial changes secondary to an old peptic ulcer.

A diagnosis of obstructive jaundice secondary either to a stone in the common bile duct or to a neoplasm of the head of the pancreas was made, and on November 3 an exploratory laparotomy was performed. The gallbladder was markedly distended and the common duct enlarged. The head of the pancreas was very hard and was two to three times the normal size. A biopsy specimen was taken from the pancreas and a cholecystogastrostomy performed after the gallbladder had been emptied of a large quantity of very viscid black bile. The patient made an uneventful convalescence except for the development of a pancreatic fistula. On microscopic examination the specimen removed from the pancreas was reported to be normal.

Experimental Procedure.—The response to various foods and to a number of excitatory and inhibitory drugs was determined. In these experiments the fluid was collected in graduated test tubes, the volume of secretion being measured and recorded at five minute intervals. The patient fasted for at least four hours before beginning any experiment.

Results.—The average output was estimated at 150 cc. per twenty-four hours. The fluid was odorless and opalescent and had a specific gravity of 1.010 and a p_H of 8.4. Inactive trypsin, lipase and amylase were present.

The effect of various diets and foodstuffs on the secretion of pancreatic juice is shown in chart 1.

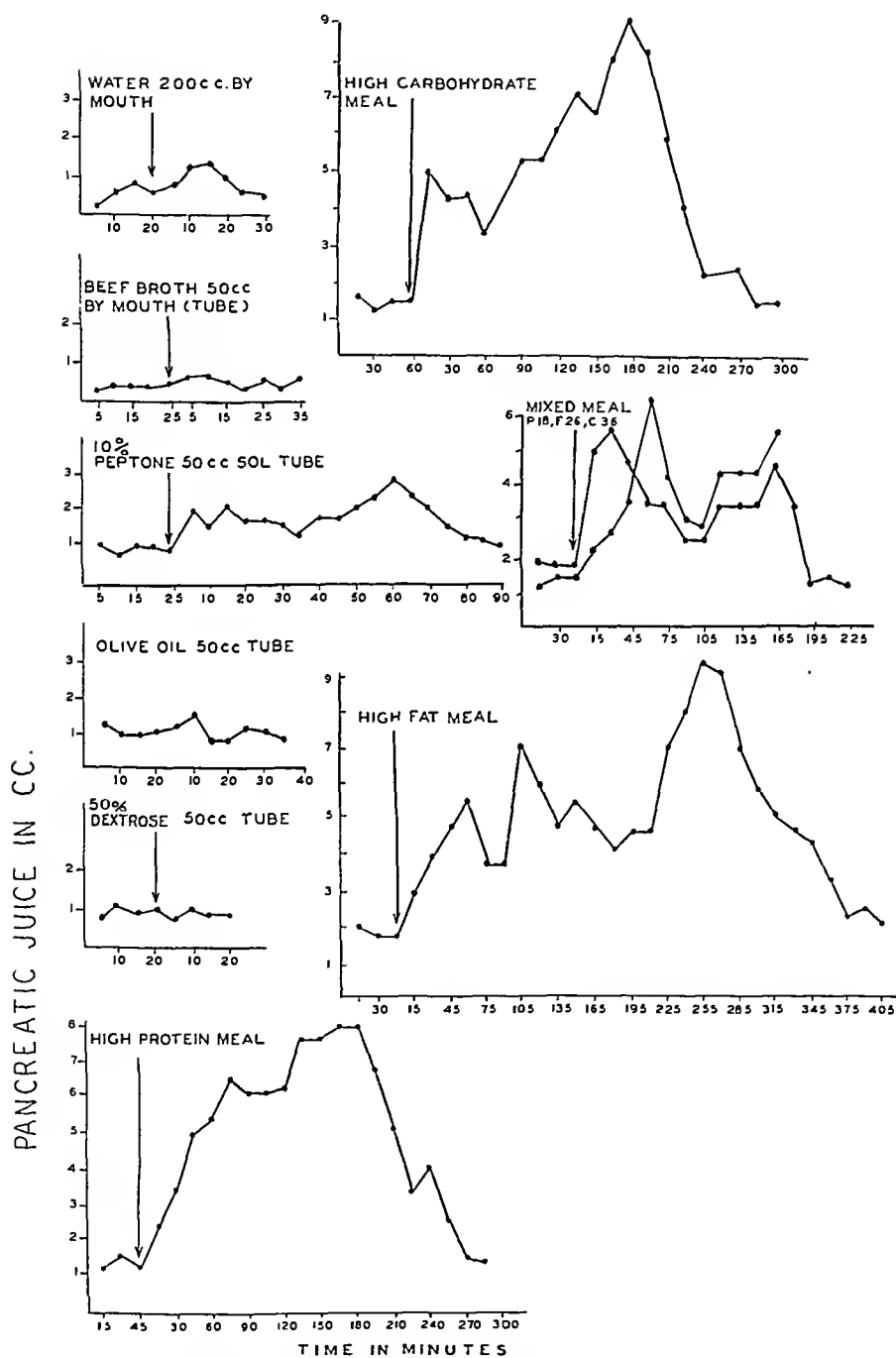


Chart 1.—The effect of various diets and foodstuffs on the secretion of pancreatic juice.

1. Diets: A diet high in fat, one high in protein, one high in carbohydrate and one which was average, or "mixed," were given. In each instance there was an immediate response characterized by a sharp increase in the flow of pancreatic juice, and in each this increased flow was maintained for three or more hours. The high fat diet resulted in the most prolonged effect as well as in the maximum output. The carbohydrate and high protein diets caused their maximum rise sooner, but the flow returned to normal earlier. The mixed diet, consisting of

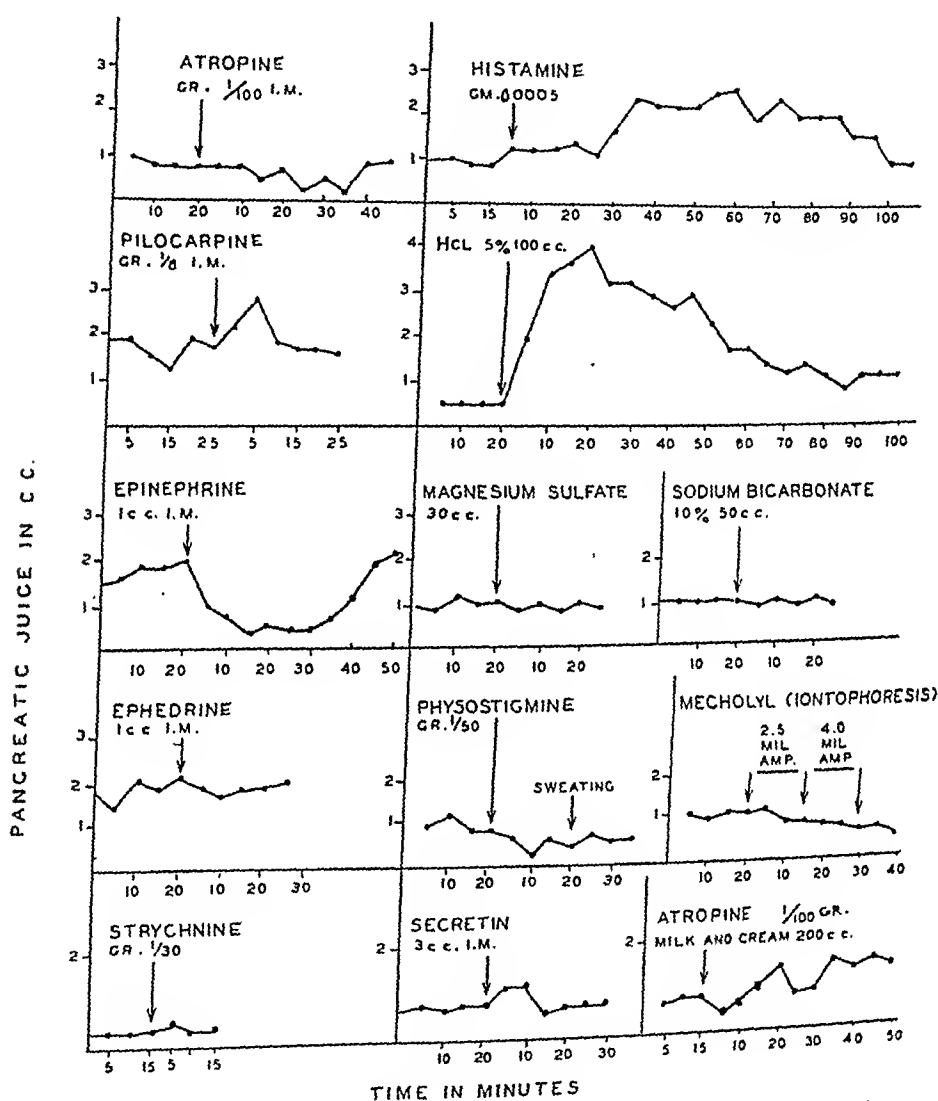


Chart 2.—The effect of various drugs on the secretion of pancreatic juice.

18 Gm. of protein, 26 Gm. of fat and 36 Gm. of carbohydrate, caused its maximum peak of secretory output sooner than any of the others, but the peak was lower and the total output was not as large.

2. Administration of Water: When 200 cc. of water was given by mouth there was an immediate increase in flow, which reached a maximum in fifteen minutes; the flow returned to normal ten minutes later.

3. Beef Broth: When 50 cc. of beef broth was given through a duodenal tube only a slight increase in flow resulted, considerably less in volume and duration than that produced by water.

4. Peptone: When 50 cc. of 10 per cent peptone solution was similarly given by tube, the response was an immediate rise, which attained its maximum in one hour. The height of the curve was somewhat greater than that in the experiment with water, and the effect was more prolonged.

5. Olive Oil: Fifty cubic centimeters of olive oil was given by intubation. The effect on flow of pancreatic juice was rather slight both as to the volume secreted and as to the duration of action. This result is contrary to that noted in case 5, in which olive oil caused a substantial increase in secretion.

6. Dextrose: Fifty cubic centimeters of a 50 per cent dextrose solution was given by the duodenal tube. The effect on the flow of pancreatic juice was negligible.

The effect of various drugs on pancreatic juice is shown in chart 2.

Effect of Various Drugs and Foodstuffs in Two Cases

Drugs or Food Administered	Secretory Response in Case 5	Secretory Response in Case 6
High protein diet.....	*	+
High fat diet.....	*	+
High carbohydrate diet.....	*	+
Mixed diet.....	+	+
Olive oil.....	+	+
Beef broth.....	+	+
Dextrose.....	+	+
Coffee.....	+	*
Peptone.....	+	+
Water.....	+	+
Secretin.....	+	+
Sodium bicarbonate.....	—	0
Strychnine.....	*	+
Ephedrine.....	*	—
Epinephrine.....	—	—
Histamine.....	—	+
Magnesium sulfate.....	—	0
Bile salts.....	—	*
Atropine.....	—	—
Physostigmine.....	+	—
Pilocarpine.....	—	+
Acetylcholine hydrochloride (meholyl).....	+	—

+ = rise; — = fall; 0 = no effect; * = not done.

1. Atropine: Atropine sulfate ($\frac{1}{100}$ grain [0.6 mg.]) given intramuscularly caused a definite lowering in the amount of secretion. This result is similar to that obtained in case 5. When a mixture of milk and cream (200 cc.) was given by mouth and $\frac{1}{100}$ grain of atropine sulfate was injected simultaneously, the inhibitory effect was less pronounced and the output of pancreatic juice increased gradually, but the response to the food was not nearly as marked as in any of the preceding feeding experiments.

2. Pilocarpine: The intramuscular injection of $\frac{1}{8}$ grain (8 mg.) of pilocarpine hydrochloride caused a definite and immediate increase in output.

3. Epinephrine: When 1 cc. of epinephrine hydrochloride was injected into the muscle the flow of pancreatic juice was promptly inhibited and remained depressed for almost an hour.

4. Ephedrine: One cubic centimeter of 5 per cent ephedrine hydrochloride solution was administered intramuscularly. There was a slight fall in the output of pancreatic juice, but the inhibitory effect was far less than was noted after administration of epinephrine.

5. Strychnine: The intramuscular injection of $\frac{1}{30}$ grain (2 mg.) of strychnine sulfate had no appreciable effect after twenty minutes of observation.

6. Histamine: Histamine phosphate was injected intramuscularly in a dose of 0.0005 Gm. There was a gradual rise to a maximum, which was attained forty minutes after the injection; then a gradual fall took place, which was not reached until one hour and forty-five minutes after the injection.

7. Physostigmine: Intramuscular injection $\frac{1}{50}$ grain (1.2 mg.) of physostigmine salicylate caused a fall in the amount of secretion accompanied with marked sweating twenty minutes after the administration of the drug.

8. Secretin: Secretin prepared by us after the method of Weaver, Luckhardt and Koch was given intramuscularly in 3 cc. doses. The response was an immediate increase in output, but the degree of rise was not striking. This, however, is probably attributable to the small dose administered.

9. Magnesium Sulfate: Thirty cubic centimeters of a saturated solution of magnesium sulfate was given through a duodenal tube. There was no significant change in the rate of flow.

10. Sodium Bicarbonate: Fifty cubic centimeters of a 10 per cent solution of sodium bicarbonate had no appreciable effect on the output of pancreatic juice.

11. Mecholyl: One-tenth per cent mecholyl chloride was given by iontophoresis with 25 to 40 milliamperes of current. An inhibition in secretion was obtained. This effect was quite the opposite to that obtained in case 5, in which the same dose and the same method of administration caused a striking increase in the output of juice.

Studies on concentration of the pancreatic enzyme were not made.

The accompanying table shows the comparative results in cases 5 and 6.

ETIOLOGY, DIAGNOSIS AND TREATMENT

Perhaps the earliest case of pancreatic fistula recorded was that of Rommelaere¹¹ in 1877. Numerous case reports have appeared in the literature since that time. Fistula of the pancreas arises in various ways. It frequently follows drainage operations on the pancreas for acute inflammatory conditions, but, according to Körte,¹² it is fairly rare as a result of a stab or a gunshot wound of the abdomen. The protected anatomic location of the pancreas is the greatest safeguard against a traumatic insult of this sort,¹³ but von Garré's¹⁴ famous case

11. Rommelaere: Rapport la commission chargée de l'examen de la communication de M. le docteur Lecompte, intitulée: Observation d'une fistule pancréatique chez l'homme, Bull. Acad. roy. de méd. de Belgique 9:1023-1042, 1877.

12. Körte, W.: Verletzungen und chirurgische Krankheiten der Leber, der Gallenblase, des Pankreas und der Milz, in Diagnostische und therapeutische Irrtümer und deren Verhütung in der Chirurgie, Leipzig, Georg Thieme, 1923, no. 3.

13. Karewaki, F.: Ueber isolierte subkutane Verletzungen des Pankreas und deren Behandlung, Berl. klin. Wchnschr. 44:187-191, 1907.

14. von Garré, C.: Totaler Querriss des Pankreas durch Naht geheilt, Beitr. z. klin. Chir. 46:233-340, 1905.

of complete transverse division of the body of the pancreas with recovery following accurate suture of the duct and parenchyma is classic. Injury to the pancreas may follow operation on the biliary tract for retroperitoneal tumor or operation on the adrenals, kidneys, spleen, stomach¹⁵ or duodenum.¹⁶ In recent years several cases of pancreatic fistula have been reported in which the condition followed partial resection of the pancreas or the excision of islet cell tumors for the relief of hyperinsulinism.¹⁷

A fistula may also follow an operation for calculi of the pancreatic duct, but probably the commonest source is a cyst of the pancreas. It is seldom possible to extirpate such a cyst, because of the difficulty of securing a satisfactory line of cleavage for dissection between the walls of the cyst and the adjacent organs, namely, the stomach, colon, great vessels and omentum. Marsupialization or drainage by tube is most often resorted to, and discharge of pancreatic juice for a variable period usually follows. Judd, Mattson and Mahorner,¹⁸ in a report of 33 cases of pancreatic cyst treated by marsupialization, stated that the discharge continued for periods varying from a few weeks to two years. None of their patients required further treatment.

The recognition of uncomplicated pancreatic fistula is not difficult. Examination of the fluid for its reaction and enzyme content establishes the diagnosis. A duodenal fistula may be differentiated by the additional presence of bile and by the erosion of the wound margins.¹⁹ Greater difficulty may be experienced in recognizing a pancreatic fistula when it is associated with a biliary fistula, as was pointed out by Popper.²⁰

The first complication of treatment of complete external pancreatic fistula is the necessity of restoring pancreatic juice to the body in sufficient quantity and before serious physiologic disturbances have taken place. Hartmann and Elman²¹ and one of us (McCaughan²²) have

15. Mayo, W. J.: The Surgery of the Pancreas, *Ann. Surg.* **58**:145-150, 1913.

16. Young, H. H., and Davis, D. M.: *Young's Practice of Urology*, Philadelphia, W. B. Saunders Company, 1926, vol. 2, p. 738.

17. Whipple, A. O., and Frantz, V. K.: Adenoma of Islet Cells with Hyperinsulinism, *Ann. Surg.* **101**:1299-1335, 1935.

18. Judd, E. S.; Mattson, H., and Mahorner, H. R.: Pancreatic Cysts: Report of Forty-Seven Cases, *Arch. Surg.* **22**:838-849 (May) 1931.

19. Garis, R. W., and Merkel, W. C.: The Symptom-Complex of Complete External Pancreatic Fistula, *Surg., Gynec. & Obst.* **39**:590-597, 1934.

20. Popper, H. L.: Pankreasfermente in der Galle, *Zentralbl. f. Chir.* **56**: 2515-2517, 1929.

21. Hartmann, A. F., and Elman, R.: Loss of Gastric and Pancreatic Secretions, *J. Exper. Med.* **50**:387-405, 1929.

22. McCaughan, J. M.: Experimental Studies on the External Secretion of the Pancreas with Special Reference to Its Complete Loss by Permanent Pancreatic Fistula, *Am. J. Physiol.* **97**:459-466, 1931.

demonstrated some of the factors concerned in the mechanism of death from total pancreatic fistula in experimental animals, and one of us (McCaughan) has noted the beneficial action of daily administration of sodium chloride intravenously and the restoration of the pancreatic juice by gastric intubation in prolonging the life of an animal with total pancreatic fistula.

The treatment of pancreatic fistula is secondarily concerned with the attempts at closure of the fistulous tract. Conservative means should always be adopted in the beginning. The clinical investigations of Wohlgemuth²³ have laid the basis for this line of treatment, which consists in the administration of a low carbohydrate diet rich in alkaline foods, large doses of sodium bicarbonate and belladonna. Wohlgemuth based his therapeutic regimen on the investigations of Pavlov,⁴ who had noted that entrance of the acid gastric juice into the duodenum invariably provokes an increased flow of pancreatic juice. Wohlgemuth's measures were therefore designed to inhibit the rate of pancreatic secretion as much as possible. Heineke,²⁴ Hohmeier²⁵ and Schmidt²⁶ obtained satisfactory results with Wohlgemuth's regimen in cases of their own. Heineke in addition advocated aspiration of the fistula by means of a catheter and a suction pump. Kroiss²⁷ recommended the administration of a water-free preparation of erepton, given in 50 Gm. doses by mouth or by rectum. Ortlisch²⁸ stated that he injected astringents and corrosives, such as tincture of iodine, silver nitrate and zinc chloride. Potter²⁹ applied tenth-normal hydrochloric acid to the fistulous tract by means of a dropper and in the intervals kept pledgets

23. Wohlgemuth, J.: Untersuchungen über das Pankreas, des Menschen. Einfluss der Zusammensetzung der Nahrung auf die Saftmenge und die Fermentconcentration, Berl. klin. Wchnschr. 44:47, 1907; Zur Therapie der Pankreasfistel, nebst Bemerkungen über den Mechanismus der Pankreassekretion während der Verdauung. *ibid.* 45:389-393, 1908; Beitrag zur funktionellen Diagnostik des Pankreas, *ibid.* 47:92-95, 1910.

24. Heineke, H.: Zur Behandlung der Pankreasfisteln, Zentralbl. f. Chirurg. 34:256-296, 1907.

25. Hohmeier, F.: Isolierte subkutane Querzerreissung des Pankreas durch Operation geheilt, München. med. Wchnschr. 54:2036-2037, 1907.

26. Schmidt, W.: Ein Fall von Totalexstirpation einer Pankreaszyste, München. med. Wchnschr. 54:2480-2482, 1907.

27. Kroiss, F.: Ein Beitrag zur Behandlung der subkutanen Duodenum und Pankreaszerreissung, Beitr. z. klin. Chir. 76:477-495, 1911. Erepton is a preparation obtained by the action of intestinal and pancreatic ferments on fat-free meat.

28. Ortlisch, cited by Kleinschmidt.⁴⁰

29. Potter, C.: Treatment of Duodenal, High Intestinal and Pancreatic Fistulas, J. Missouri M. A. 29:374, 1932.

of gauze soaked in a solution of peptone in the cutaneous opening of the fistula. In addition to the secretory inhibitants noted, our own investigations (see table) indicated the value of adding epinephrine and ephedrine to the therapeutic armamentarium.

The use of high voltage roentgen therapy was reported as successful by Culler³⁰ in the cases of 2 soldiers with pancreatic fistula. In each patient the fistula was said to have closed completely after five treatments. Orndoff, Tarrell and Ivy,³¹ on the other hand, studied the effects of roentgen rays on the pancreases of laboratory animals and concluded that, while the pancreas could be temporarily injured, its power of regeneration later overcompensated and the total output of ferments might even become greater than normal. Our own experience in giving high voltage roentgen therapy to a patient with a pancreatic fistula is in accord with the conclusions of Orndoff, Tarrell and Ivy. We exposed the left upper quadrant of the abdomen to a current of 200 kilowatts and 5 milliamperes for fifteen minutes at a time, giving a total exposure of seventy-five minutes. There was no noticeable improvement, and surgical incision and drainage later became imperative.

If these conservative methods fail after trial for a reasonable period, radical measures should be considered. Excision or extirpation of the entire fistulous tract, for obvious reasons, is rarely possible. In 1905, Doyen³² reported the first instances of successful implantation of the pancreatic duct into the greater curvature of the stomach after resection of the papilla of Vater for carcinoma. Kausch³³ in 1909 reported the successful implantation of the stump of the pancreas into the duodenum, also after a resection of a carcinoma of the papilla of Vater. The experimental work of Coffey,³⁴ Desjardins³⁵ and Faykiss³⁶ on pancreatico-enterostomy was an important forward step in this difficult field of surgical technic. Following the work of Doyen and Kausch on the transplantation of the pancreatic duct after resection of the papilla of

30. Culler, R. M.: Cure of Pancreatic Fistula by the Roentgen Ray, J. A. M. A. **75**:20 (July 3) 1920.

31. Orndoff, B. H.; Tarrell, J. J., and Ivy, A. C.: Studies on the Effect of Roentgen Rays on Glandular Activity: V. The Effect of Roentgen Rays on External Pancreatic Section, Am. J. Roentgenol. **16**:349-354, 1926.

32. Doyen, cited by Kleinschmidt.⁴⁰

33. Kausch, W.: Die Resektion des mittleren Duodenum, Zentralbl. f. Chir. **36**:1350-1376, 1909.

34. Coffey, B. C.: Pancreato-Enterostomy and Pancreatectomy, Ann. Surg. **50**:1238-1264, 1909.

35. Desjardins, cited by Kleinschmidt.⁴⁰

36. Faykiss, F.: Ueber experimentelle Pankreasresektion und Pankreatoenterostomie, Beitr. z. klin. Chir. **84**:188-200, 1913.

Water for carcinoma, others began to utilize the principle of this method in dealing with intractable fistulas of the pancreas, particularly Jedlicka³⁷ (1921), Lorenz³⁸ (1921), Hammesfahr³⁹ (1923), Kleinschmidt⁴⁰ (1925), Corachan⁴¹ (1924), Cathala and Sèneque⁴² (1930) and Janes⁴³ (1934).

The technic of fistula transplantation consists in making a careful dissection of the fibrous fistulous tract until a sufficient length has been mobilized. This should then be implanted without tension or angulation into the nearest portion of the upper part of the gastro-intestinal tract, preferably the stomach. A tag of fat from the round ligament, the gastrocolic or the gastrohepatic omentum or even a free graft of fat is stitched about the site of implantation to protect the line of suture against leakage. A small drainage tube is placed near the site of operation, to be removed in twenty-four hours, and the abdominal wound is closed in the usual manner.

SUMMARY

The experimental background of animal work on pancreatic fistula is briefly mentioned. A more detailed account of clinical and experimental observations on 6 patients with pancreatic fistulas is given. Two of the fistulas resulted from external trauma; 1 followed acute pancreatic necrosis, and 3 developed after abdominal operations, 1 of the 3 last mentioned being also associated with a pancreatic cyst.

Physiologic investigations on the external secretory function were carried out in 2 of the cases, and the effect on the secretory rate was recorded after the administration of a variety of drugs and foodstuffs.

From a practical clinical standpoint the management of an uncomplicated pancreatic fistula, particularly if the drainage of pancreatic

37. Jedlicka, R.: Zur Operation der Pancreaskysten, Zentralorg. f. d. ges. Chir. u. Grenzgeb. **16**:153, 1922.

38. Lorenz: Kasuistische Beiträge zur Pankreas und zur Gallenchirurgie, Wien. klin. Wchnschr. **28**:339-340, 1921.

39. Hammesfahr, C.: Zur Behandlung von Pankreasfisteln, Zentralbl. f. Chir. **50**:1758-1759, 1923.

40. Kleinschmidt, O.: Behandlung der Fisteln des Pankreas und des Ductus pankreaticus, Arch. f. klin. Chir. **135**:363-372, 1925.

41. Corachan, M.: Sur le traitement des fistules pancréatiques, Presse méd. **36**:1394-1397, 1928.

42. Cathala, J., and Sèneque, J.: Fistule pancréatique réinjection du suc pancréatique, amélioration, pancréatico-gastrostomie, Guérison, Presse méd. **38**:1534-1537, 1930.

43. Janes, R. M.: Pancreatic Fistula: Report of a Case; Cure by Pancreatogastrostomy, Brit. J. Surg. **22**:296-300, 1934.

juice is great, resolves itself into (1) preventing or replacing the loss of electrolytes, fluid and protein and (2) carrying out measures directed toward encouraging spontaneous closure. According to our studies, a "mixed diet" provokes less drainage than does one predominantly high in one or other of the three foodstuffs. Fats particularly seemed an effective secretory stimulus. Certain drugs were found to inhibit secretion; these were principally atropine, sodium bicarbonate, ephedrine and epinephrine. High voltage roentgen therapy was without value.

In the great majority of cases a pancreatic fistula will close in time, but infection must be avoided and the surrounding skin given special protective care. If spontaneous closure fails after a sufficient time the fistula may be reimplanted into the upper part of the gastrointestinal tract with little risk and a reasonable likelihood of success.

THE SYMPATHETIC NERVOUS SYSTEM IN NEUROGENIC AND RENAL HYPERTENSION

EXPERIMENTAL CORRELATION AND CLINICAL CONSIDERATION

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The development in the last eight years of various surgical technics directed toward alleviation of essential, or idiopathic, hypertension has renewed interest in the role of the sympathetic nervous system and its splanchnic divisions in regulation of blood pressure and their possible etiologic role in clinical hypertension. These surgical technics have been chiefly directed toward sympathetic denervation of the splanchnic area. It is difficult to evaluate the therapeutic effect of these procedures and even more difficult to estimate whether the improvements reported are related to an elimination of etiologic factors or to a direct effect produced by denervation of large vascular beds. The experiments to be considered in this study deal with an attempt to reexamine the role of the sympathetic nervous system and its splanchnic divisions in regulation of blood pressure. The possible role of the sympathetic system in the production of chronic neurogenic hypertension in man is also discussed.

It is accepted that the major factor of both experimental and clinical hypertension is an increase in peripheral resistance and that in an advanced stage of hypertension this may be chiefly maintained in some instances by pathologic changes in the blood vessels, including the arterioles. A review of renal and neurogenic factors which may initiate an increase of peripheral resistance is undertaken.

RENAL HYPERTENSION

It has been established that the kidney under certain experimental and clinical conditions of altered blood flow may by a humoral mechanism produce hypertension. Goldblatt and his associates¹ were mainly responsible for the experimental demonstration that the kidney may initiate hypertension. The development of an understanding of the

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1. Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Sommerville, W. W.: The Production of Persistent Hypertension in Dogs, *Am. J. Path.* 9:942, 1933.

mechanism of this hypertension has been extensively reviewed in recent literature (Katz and co-workers²; Page³; Pickering⁴; Goldblatt⁵; Blalock⁶; and others). The demonstration that the hypertension which follows partial obstruction of the renal artery persists after complete sympathectomy (Heymans, Bouckaert, Elaut, Bayless and Samaan⁷; Freeman and Page⁸; Alpert, Alving and Grimson⁹; Verney and Vogt¹⁰) and after complete transplantation of the kidney (Dicker¹¹; Glenn, Child and Heuer¹²; Blalock and Levy¹³) contributes, together with other accumulating indirect evidence, to the conclusion that this renal type of hypertension is effected through the blood stream and not through the nervous system. Evidence has been presented that extracts of kidneys with partial obstruction of the renal arteries contain increased amounts of renin (Harrison, Blalock and Mason¹⁴; Prinzmetal and

2. Katz, L. N.; Friedman, M.; Rodbard, S., and Weinstein, W.: Observations on the Genesis of Renal Hypertension, *Am. Heart J.* **17**:334, 1939.

3. Page, I. H.: *Newer Aspects of Experimental Hypertension*, in *Blood, Heart and Circulation*, Publication 13, American Association for the Advancement of Science, 1940, p. 239.

4. Pickering, G. W.: The Problem of High Blood Pressure in Man, *J. Mt. Sinai Hosp.* **5**:649, 1939.

5. Goldblatt, H.: Studies on Experimental Hypertension, *Am. J. Clin. Path.* **10**:40, 1940.

6. Blalock, A.: Experimental Hypertension, *Physiol. Rev.* **20**:159, 1940.

7. Heymans, C.; Bouckaert, J. J.; Elaut, W.; Bayless, F., and Samaan, A.: Hypertension artérielle chronique par ischémie rénale chez le chien totalement sympathectomisé, *Compt. rend. Soc. de biol.* **126**:434, 1937.

8. Freeman, N. E., and Page, I. H.: Hypertension Produced by Constriction of the Renal Artery in Sympathectomized Dogs, *Am. Heart J.* **14**:405, 1937.

9. Alpert, L. K.; Alving, A. S., and Grimson, K. S.: Effect of Total Sympathectomy on Experimental Renal Hypertension in Dogs, *Proc. Soc. Exper. Biol. & Med.* **37**:1, 1937.

10. Verney, E. B., and Vogt, M.: An Experimental Investigation into Hypertension of Renal Origin with Some Observations on Convulsive "Uraemia," *Quart. J. Exper. Physiol.* **28**:253, 1938.

11. Dicker, E.: Résultats de l'anastomose de reins normaux au cou de chiens hypertendus par compression de leurs artères rénales, *Compt. rend. Soc. de biol.* **126**:912, 1937.

12. Glenn, F.; Child, C. G., and Heuer, G. J.: Production of Hypertension by Constricting the Artery of a Single Transplanted Kidney, *Ann. Surg.* **106**:848, 1937.

13. Blalock, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, *Ann. Surg.* **106**:826, 1937.

14. Harrison, T. R.; Blalock, A., and Mason, M. F.: Effects on Blood Pressure of Injection of Kidney Extracts of Dogs with Renal Hypertension, *Proc. Soc. Exper. Biol. & Med.* **35**:38, 1936.

Friedman¹⁵). Kohlstaedt and Page¹⁶ have described the liberation of renin by excised kidneys artificially perfused when the arteries are clamped and the pulse pressure reduced. Prinzmetal, Lewis and Leo¹⁷ have reported increased amounts of renin in perfusates of kidneys obtained after approximately five hours of total ischemia. The demonstration (Houssay and Fasciolo¹⁸) that a kidney or kidneys which after partial obstruction of the renal arteries have produced chronic hypertension in 1 dog can when transplanted into the circulation of a second dog elevate its blood pressure affords direct physiologic evidence that a hypertensive substance is liberated by the kidney. This important observation has been confirmed by Dicker,¹¹ Bouckaert, Heymans and me¹⁹ and by Lewis, Leo and Prinzmetal.²⁰

A possible renal source of this renal pressor substance has been suggested by the observation after partial obstruction of renal arteries in dogs and rabbits of cellular hypertrophy, vacuolation and even mitosis in the groups of large afibrillar cells normally present in the media of the arteries that make up the juxtaglomerular apparatus (Goormaghtigh and Grimson²¹; and Goormaghtigh²²). Cells of this type are also present elsewhere in the body.

Page and Helmer²³ have contributed, as a result of a long series of experiments, a new concept of the mechanism by which blood pressure is

15. Prinzmetal, M., and Friedman, B.: Pressor Effects of Kidney Extracts from Patients and Dogs with Hypertension, *Proc. Soc. Exper. Biol. & Med.* **35**:122, 1936.

16. Kohlstaedt, K. G., and Page, I. H.: The Liberation of Renin by Perfusion of Kidneys Following Reduction of Pulse Pressure, *J. Exper. Med.* **72**:201, 1940.

17. Prinzmetal, M.; Lewis, H. A., and Leo, S. D.: The Etiology of Hypertension Due to Complete Renal Ischemia, *J. Exper. Med.* **72**:763, 1940.

18. Houssay, B. A., and Fasciolo, J. C.: Demostración del mecanismo humoral de la hipertensión nefrógena, *Bol. Acad. nac. de med. Buenos Aires*, 1937, p. 342.

19. Bouckaert, J. J.; Grimson, K. S., and Heymans, C.: Increase of Blood Pressure by Perfusion of the Ischaemic Kidneys of Hypertensive Dogs, *J. Physiol.* **96**:45P, 1939.

20. Lewis, H. A.; Leo, S. D., and Prinzmetal, M.: *Am. Heart J.*, to be published.

21. Goormaghtigh, N., and Grimson, K. S.: Vascular Changes in Renal Ischemia Cell Mitosis in the Media of Arteries, *Proc. Soc. Exper. Biol. & Med.* **42**:227, 1939.

22. Goormaghtigh, N.: Histological Changes in the Ischemic Kidney, *Am. J. Path.* **16**:409, 1940.

23. Page, I. H., and Helmer, O. M.: A Crystalline Pressor Substance (Angiotonin) Resulting from the Reaction Between Renin and Renin-Activator, *J. Exper. Med.* **71**:29, 1940; Angiotonin-Activator, Renin- and Angiotonin-Inhibitor, and the Mechanism of Angiotonin Tachyphylaxis in Normal, Hypertensive, and Nephrectomized Animals, *ibid.* **71**:495, 1940.

elevated in "renal" hypertension. They have postulated the existence of a pressor substance, angiotonin, resulting from the reaction between renin and renin activator, and the existence of an angiotonin inhibitor. A parallel series of observations has been recently reported by Munoz, Braun-Menendez, and Fasciolo and Leloir,²⁴ who used the terms hypertension precursor, hypertensin and hypertensinase.

Grollman, Williams, and Harrison²⁵ and Page, Helmer, Kohlstaedt, Fouts, Kempf and Corcoran²⁶ have reported reductions of blood pressure in patients and in animals with renal hypertension by the use of renal extracts. It is too early to evaluate these important observations accurately or to predict the extent to which renal extracts may ultimately be employed in the clinical treatment of hypertension.

The relation of the renal type of experimental hypertension to essential, or idiopathic, hypertension in man has been greatly emphasized. It is possible by proper adjustment of the renal artery clamps to produce a form of chronic hypertension with little evidence of deficient renal function, which may be likened to essential hypertension. It is also possible by more severe obstruction to produce changes that resemble the clinical picture of malignant hypertension. In those instances of clinical hypertension in which there is evident pathologic alteration in the renal arteries or in the kidney that may have altered the renal hemodynamics, one can postulate the existence of a hypertensive mechanism similar to that of experimental renal hypertension. Reports of hypertension in patients with unilateral renal disease and of relief following unilateral nephrectomy apparently substantiate this hypothesis. In many more instances, especially of the earlier types of clinical hypertension, it is more difficult to postulate a mechanism by which renal hemodynamics may be altered. It has been suggested by Peet, Woods and Braden²⁷ and others that an overactivity of the renal sympathetic vasoconstrictor nerves may initiate the process. Moritz and Oldt²⁸ have reported the observation at autopsy of marked renal arteriolar sclerosis

24. Fasciolo, J. C., and Leloir, L. F.: The Mechanism of Renal Hypertension, *Am. J. M. Sc.* **200**:608, 1940.

25. Grollman, A.; Williams, J. R., and Harrison, T. R.: Reduction of Elevated Blood Pressure by Administration of Renal Extracts, *J. A. M. A.* **115**:1169 (Oct. 5) 1940.

26. Page, I. H.; Helmer, O. M.; Kohlstaedt, K. G.; Fouts, G. F.; Kempf, G. F., and Corcoran, A. C.: Substance in Kidneys and Muscle Eliciting Prolonged Reduction of Blood Pressure in Human and Experimental Hypertension, *Proc. Soc. Exper. Biol. & Med.* **43**:722, 1940.

27. Peet, M. M.; Woods, W. W., and Braden, S.: The Surgical Treatment of Hypertension, *J. A. M. A.* **115**:1875 (Nov. 30) 1940.

28. Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, *Am. J. Path.* **13**:679, 1937.

in patients who died of hypertension. This was found only occasionally in the kidneys of patients who died without hypertension. These authors have suggested that arteriolar disease occurring primarily in the kidneys may initiate a Goldblatt clamp type of renal hypertension in man. It is of interest that the incidence of renal arteriolar sclerosis greatly exceeded that of arteriolar sclerosis elsewhere in the body only in those patients who died from renal failure and were classified as having had malignant hypertension. Patients with hypertension of a more benign and chronic course who ultimately died of cerebral hemorrhage or cardiac failure had about the same amount of arteriolar sclerosis in the kidneys as in the spleen, pancreas, adrenal glands, gastrointestinal tract and skeletal muscles. The observation that there was less arteriolar sclerosis in the kidneys of patients without hypertension than in other tissues of the same patients is not clearly understood.

Clinical efforts to treat essential hypertension directed toward a renal factor either by division of the splanchnic nerves (Peet, Woods and Braden²⁷ and many others) or by the removal of unilateral diseased kidneys (Braasch, Walters and Hammer²⁹; Crabtree and Chaset,³⁰ and others) have in many instances been disappointing. It is entirely possible that the renal factor may be primary only in a certain group of hypertensive patients and that other factors may be primary in other groups, in which there may be no evidence of renal change in the early stage of the disease.

NEUROGENIC HYPERTENSION

Many observers of essential hypertension have stressed the importance of the emotional or psychologic status of their patients (Stewart,³¹ Katz and Leiter³²; Alexander³³; Weiss³⁴; Robinson³⁵; Gilbert,³⁶ and

29. Braasch, W. A.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, *J. A. M. A.* **115**:1837 (Nov. 30) 1940.

30. Crabtree, E. G., and Chaset, N.: Vascular Nephritis and Hypertension, *J. A. M. A.* **115**:1842 (Nov. 30) 1940.

31. Stewart, H. J.: The Management of Hypertension, *Bull. New York Acad. Med.* **14**:681, 1938.

32. Katz, L. N., and Leiter, L.: The Present Conception of "Essential" Hypertension, *Psychosom. Med.* **1**:101, 1939.

33. Alexander, F.: Emotional Factors in Essential Hypertension: Presentation of a Tentative Hypothesis, *Psychosom. Med.* **1**:173, 1939.

34. Weiss, E.: Recent Advances in the Pathogenesis and Treatment of Hypertension, *Psychosom. Med.* **1**:180, 1939.

35. Robinson, S. K.: A Comparison of the Medical and Surgical Treatment in Hypertension with Special Reference to the Importance of Psychic Factors in Evaluating the Results, with a Report of Ninety-Two Cases Treated Medically, *J. Nerv. & Ment. Dis.* **91**:157, 1940.

36. Gilbert, N. C.: Hypertension, *Northwest Med.* **39**:202 and 255, 1940.

others). Recognition of psychosomatic factors with evidence of psychomotor and psychovasomotor overactivity and reports of improvement following environmental change, psychotherapy and sedation point to the existence of a type of hypertension in which neurogenic factors are important. Vasomotor instability evidenced by abnormally high responses to the "cold pressor test" has been observed in a great majority of patients with essential hypertension (Hines³⁷ and others). A neurogenic type of hypertension related to vasomotor instability must, according to physiologic concepts, be reflex and effected largely if not entirely through the sympathetic nervous system. Physiologic studies related to the role of the sympathetic nervous system in the mediation of experimental central or neurogenic types of hypertension may therefore afford information related directly to the surgical treatment of essential hypertension.

Such central neurogenic types of hypertension have been described as occurring in dogs after a variety of procedures, including experimental increase of intracranial pressure, progressive ligation of cerebral arteries, injection of kaolin into the cisterna magna or the fourth ventricle and section of the modulator, buffer or regulator nerves from the pressure-sensitive areas of the carotid sinus and of the cardioaortic region. The last-mentioned procedure, since it produces an abnormality of vasomotor regulation by removing the buffer action of these nerves and thus produces a chronic and enduring type of hypertension, is well suited for these physiologic studies.

The aortic depressor nerve was described by Willis³⁸ (1664) and by Theile³⁹ (1825). The carotid sinus was noted in anatomic dissections by Meyer⁴⁰ (1875), Schäfer⁴¹ (1878) and Binswanger⁴² (1879).

37. Hines, E. A., Jr.: Significance of Vascular Hyperreaction as Measured by Cold-Pressor Test, *Am. Heart J.* **19**:408, 1940; Range of Normal Blood Pressures and Subsequent Development of Hypertension: Follow-Up Study of 1,522 Patients, *J. A. M. A.* **115**:271 (July 27) 1940.

38. Willis, T.: *De cerebri anatome nervorumque descriptio et usus*, London, J. Flesher, 1664; *Of the Description and Use of the Nerves*, translated from the Latin by S. Pordage, London, T. Dring, C. Harper, J. Leigh, 1684.

39. Theile, F. W.: *De musculis nervisque laryngeis*, Inaug. Dissert., Jena, typ. Schreiberi et soc., 1825, p. 35.

40. Meyer, L.: Ueber aneurysmatische Veränderungen der Carotis interna Geisteskranker, *Arch. f. Psychiat.* **6**:84, 1875.

41. Schäfer: Ueber die aneurysmatischer Erweiterung der Carotis interna an ihrem Ursprung, *Allg. Ztschr. f. Psychiat.* **34**:438, 1878.

42. Binswanger, O.: Anatomische Untersuchungen über die Ursprungsstelle und den Anfangstheil der Carotis interna, *Arch. f. Psychiat.* **9**:351, 1879.

Physiologic studies of the cardioaortic depressor nerves were reported by Cyon and Ludwig⁴³ (1866), Roever⁴⁴ (1869 and Wooldridge⁴⁵ (1883). It was, however, not until the work of Hering⁴⁶ (1924) and de Castro⁴⁷ (1926) that the fundamental investigations were started which led to an understanding of the importance of these structures in the regulation of blood pressure and respiration. The first experiments suggesting that the division of these four modulator nerves, one from each carotid sinus and one alongside each vagus nerve, could cause chronic hypertension came in the reports of Koch and Mies.⁴⁸ These authors demonstrated moderate hypertension (pressure 150 to 180 mm. of mercury) following this procedure in rabbits, and later (1931) they made the same demonstration in dogs (Koch⁴⁹). Koch, working with Mattonet in 1934⁵⁰ on rabbits, cats and dogs, reversed this original statement and reported that the elevation of blood pressure does not endure but rather returns to lower levels after many months. Heymans and Bouckaert⁵¹ in 1931 presented the first of a comprehensive series of studies of chronic enduring neurogenic hypertension in dogs and reported pressures as high as 250 mm. of mercury after section of the modulator nerves. Dautrebande,⁵² in the same year, during pharmacologic studies incidentally observed elevations of blood pressure in 3 dogs

43. Cyon, E., and Ludwig, C.: Die Reflexe eines der sensiblen Nerven des Herzens auf die motorischen der Blutgefäße, *Arb. a. d. physiol. Anat. zu Leipzig* (1866), 1867, p. 128.

44. Roever, G.: Kritische und experimentelle Untersuchung des Nerveneinflusses auf die Erweiterung und Verengerung der Blutgefäße, Rostock, H. Koch, 1869.

45. Wooldridge, L.: Ueber die Function der Kammerneerven des Säugthierherzens, *Arch. f. Physiol.*, 1883, p. 522.

46. Hering, H. E.: Der Sinus caroticus, *München. med. Wchnschr.* **71**:701, 1924.

47. de Castro, F.: Glomus Caroticum, Structure, *Trab. Lab. de invest. biol., Madrid* **24**:365, 1926.

48. Koch, E., and Mies, H.: Ueber Gefäßreflexe insbesondere über die Blutdruckzügler, *Ergebn. d. ges. Med.* **13**:297, 1929; *Cronischer arterieller Hochdruck durch experimentelle Dauerausschaltung des Blutdruckzügler, Krankheitsforschung* **7**:241, 1929.

49. Koch, E.: *Ergebnisse der Kreislaufforschung*, Dresden, Theodor Steinkopff, 1931, vol. 1.

50. Koch, E., and Mattonet, K.: Versuche zur Frage der arteriellen Hypertonie nach Dauerausschaltung von pressorreceptorischen Kreislaufnerven, *Ztschr. f. d. ges. exper. Med.* **94**:105, 1934.

51. Heymans, C., and Bouckaert, J. J.: Observations chez le chien en hypertension artérielle chronique et expérimentale, *Compt. rend. Soc. de biol.* **106**:471, 1931.

52. Dautrebande, L.: Réactions vasomotrices à l'oxygène et à l'acide carbonique chez le chien en hypertension artérielle par énervation des zones vasosensibles, *Arch. internat. de pharmacodyn. et de thérap.* **40**:107, 1931.

similarly prepared. This occurrence of enduring hypertension in dogs has been repeatedly confirmed in the laboratory of Heymans⁵³ in Belgium and in the United States by Nowak and Walker,⁵⁴ Nowak⁵⁵ and me.⁵⁶

Goldblatt, Kahn, Bayless and Simon⁵⁷ and several other authors have failed to obtain this type of hypertension. A statement of observations agreed on by all who have reported positive results in dogs might aid in an evaluation of the negative results. Denervation or excision of the carotid sinuses alone will effect only transient hypertension. The modulator function is quickly taken over by the two cardioaortic depressor nerves. Denervation or excision of the carotid sinuses and division of one cardioaortic depressor nerve will also fail to produce enduring hypertension. The remaining cardioaortic depressor nerve will take over the function of the three eliminated nerves. Similarly, division of a large part of the remaining depressor nerve will frequently fail to produce chronic hypertension. In the dog the cervical sympathetic chain and the cardioaortic depressor nerve run in a single trunk, along with the vagus nerve. Frequently the separation of these structures is extremely difficult, and even by an experienced operator a portion of the depressor nerve may be overlooked or the vagus nerve may be so damaged that a general state of malnutrition accompanied with frequent vomiting follows. In either event hypertension may fail to develop. Most operators have, with increasing experience, been able to produce in dogs higher and higher percentages of substantial hypertensions.

NEUROGENIC HYPERTENSION AND THE SYMPATHETIC NERVOUS SYSTEM

Several investigations have been made to determine the relation of the sympathetic nervous system to experimental neurogenic hypertension in dogs. Bacq, Brouha and Heymans⁵⁸ reported that complete sym-

53. Personal observation made during 1938 and 1939 in the laboratory of Prof. C. Heymans, University of Ghent, Belgium.

54. Nowak, S. J. G., and Walker, I. J.: *Experimental Studies Concerning the Nature of Hypertension*, New England J. Med. **220**:269, 1939.

55. Nowak, S. J. G.: *Chronic Hypertension Produced by Carotid Sinus and Aortic-Depressor Nerve Section*, Ann. Surg. **111**:102, 1940.

56. Grimson, K. S.: *Role of the Sympathetic Nervous System in Experimental Neurogenic Hypertension*, Proc. Soc. Exper. Biol. & Med. **44**:219, 1940.

57. Goldblatt, H.; Kahn, J. R.; Bayless, F., and Simon, M. A.: *The Effect of Excision of the Carotid Sinuses on Experimental Hypertension Produced by Renal Ischemia*, J. Exper. Med. **71**:175, 1940.

58. Bacq, Z.; Brouha, L., and Heymans, C.: *Section des nerfs aortiques et sino-carotidiens chez le chien totalement sympathectomisé*, Compt. rend. Soc. de biol. **115**:1380, 1934.

pathectomy prevented the carotid sinus reflex in acute experiments in dogs but not entirely in cats. Elaut⁵⁹ observed that denervation of the kidneys in 3 dogs did not prevent or alleviate the hypertension produced by section of the depressor nerve. On a dog with experimental neurogenic hypertension Heymans and Bouckaert⁶⁰ performed total sympathectomy in the following stages: abdominal sympathectomy and resection of the splanchnic nerves; celiac and superior mesenteric ganglionectomy, and bilateral thoracic sympathectomy. The blood pressure remained at a normal level over a five day period of observation, from which they concluded that sympathectomy must be complete to abolish hypertension. These experiments have been reviewed by Heymans.⁶¹

Nowak and Walker⁵⁴ and Nowak⁵⁵ have enlarged on these studies. They reported the development of sustained hypertension in 10 dogs, the pressures ranging up to 245 mm. of mercury; the condition was observed in 1 instance for as long as three years. They reported that resection of the splanchnic nerves lowers the blood pressure only temporarily. They also reported that total sympathectomy preliminary to section of the modulator nerves fails to prevent the immediate development of a modest elevation of blood pressure. This last observation conflicts with the report of Bacq, Brouha and Hymans⁵⁸ that sympathectomy abolishes the carotid sinus reflex in dogs.

EXPERIMENTAL STUDIES

Since increasing importance is being attributed to vasomotor instability in patients with "essential hypertension," studies have been undertaken to investigate further the hypertension resulting from the disturbance of vasomotor regulation that follows section of the modulator nerves in dogs. These were performed in order to determine the role played by the sympathetic system in part and as a whole. Further studies were designed to determine whether there is a correlation between this neurogenic type of hypertension and renal hypertension. Preliminary reports of this work have been published (Grimson, Bouckaert and Heymans,⁶² Grimson⁵⁶). The experiments were performed on dogs and were of the chronic type. All blood pressures were taken by

59. Elaut, L.: Influence de l'énervation rénale sur l'hypertension expérimentale chronique chez le chien, *Compt. rend. Soc. de biol.* **119**:318, 1935.

60. Heymans, C., and Bouckaert, J. J.: Hypertension artérielle expérimentale et sympathectomie, *Compt. rend. Soc. de biol.* **120**:82, 1935.

61. Heymans, C.: Some Aspects of Blood Pressure Regulation and Experimental Arterial Hypertension, *Surgery* **4**:487, 1938.

62. Grimson, K. S.; Bouckaert, J. J., and Heymans, C.: Production of a Sustained Neurogenic Hypertension and Renal Origin, *Proc. Soc. Exper. Biol. & Med.* **42**:225, 1939.

direct puncture of the femoral artery with a needle connected to a mercury manometer.

Experimental Neurogenic Hypertension in Dogs.—Twenty-four apparently normal dogs were operated on according to the technic personally demonstrated by Bouckaert.⁶³

Technic: This consists of exposure of both carotid sinuses and the upper part of both vago-sympathetic-depressor nerve trunks at the level of the thyroid cartilage through a 3 inch (7.5 cm.) midline incision. The gray strand representing the cervical sympathetic chain is located near the superior cervical ganglion. In a few instances the whiter depressor nerve lying with it on the medial aspect of the vagus nerve is easily seen. Usually, however, it is necessary with a delicate, sharp instrument or a needle to tear apart the medial fibers of the vagus nerve up near the superior laryngeal nerve or at a level with or slightly below the carotid sinus until all strands suspected of being depressor nerve fibers are freed from the whiter vagus nerve. A segment of these is then removed. The right vagus nerve is explored first. Usually the depressor nerve and the cervical sympathetic chain on this side are cut. If, however, the dissection is obscure or the vagus nerve is damaged, exploration of the opposite vagus nerve is undertaken. In either event 1 inch (2.5 cm.) of one entire vago-sympathetic-depressor trunk and a short segment of the sympathetic depressor portion of the opposite trunk are removed. Each carotid sinus is entirely removed, a single ligature being used for its branches and another for its common carotid trunk. This procedure reduces to a minimum the dangers of overlooking portions of the modulator nerves and of nerve regeneration. The blood supply of the brain is adequately preserved through the vertebral and other collateral arteries.

Of the 24 normal dogs operated on, enduring hypertension developed in 18. Ten showed immediate hypertension, with blood pressure readings averaging more than 250 mm. of mercury during the interval (one to four months) that preceded further surgical intervention. Readings as high as 308 mm. of mercury were recorded. Four dogs had immediate elevation of blood pressure, with average readings from 200 to 250 mm. of mercury, which persisted at that level two and a half to five months before further experimental intervention. For 3 dogs the readings were below or around 200 mm. for about two months and then showed further gradual elevation, reaching in four to six months levels of about 220, 260 and 280 respectively. The blood pressure of 1 dog averaged 175 mm. of mercury, but after another operation and division of the medial third of the remaining portion of the right vagus nerve the average reading increased to 218 mm. during the following four months. A composite graph of the blood pressures of these 18 dogs is presented (chart 1).

Of the 6 remaining dogs, 1 died at the time of operation. Two died of distemper five days after the operation, without postoperative blood

63. Prof. J. J. Bouckaert of Prof. C. Heymans' Laboratory in Ghent, Belgium.

pressure readings. Two died respectively eleven and thirty-one days after the operation; the maximum blood pressure readings were 206 and 242 mm. of mercury respectively. Malnutrition and vomiting were conspicuous. One animal (dog 46) showed a gradual elevation of blood

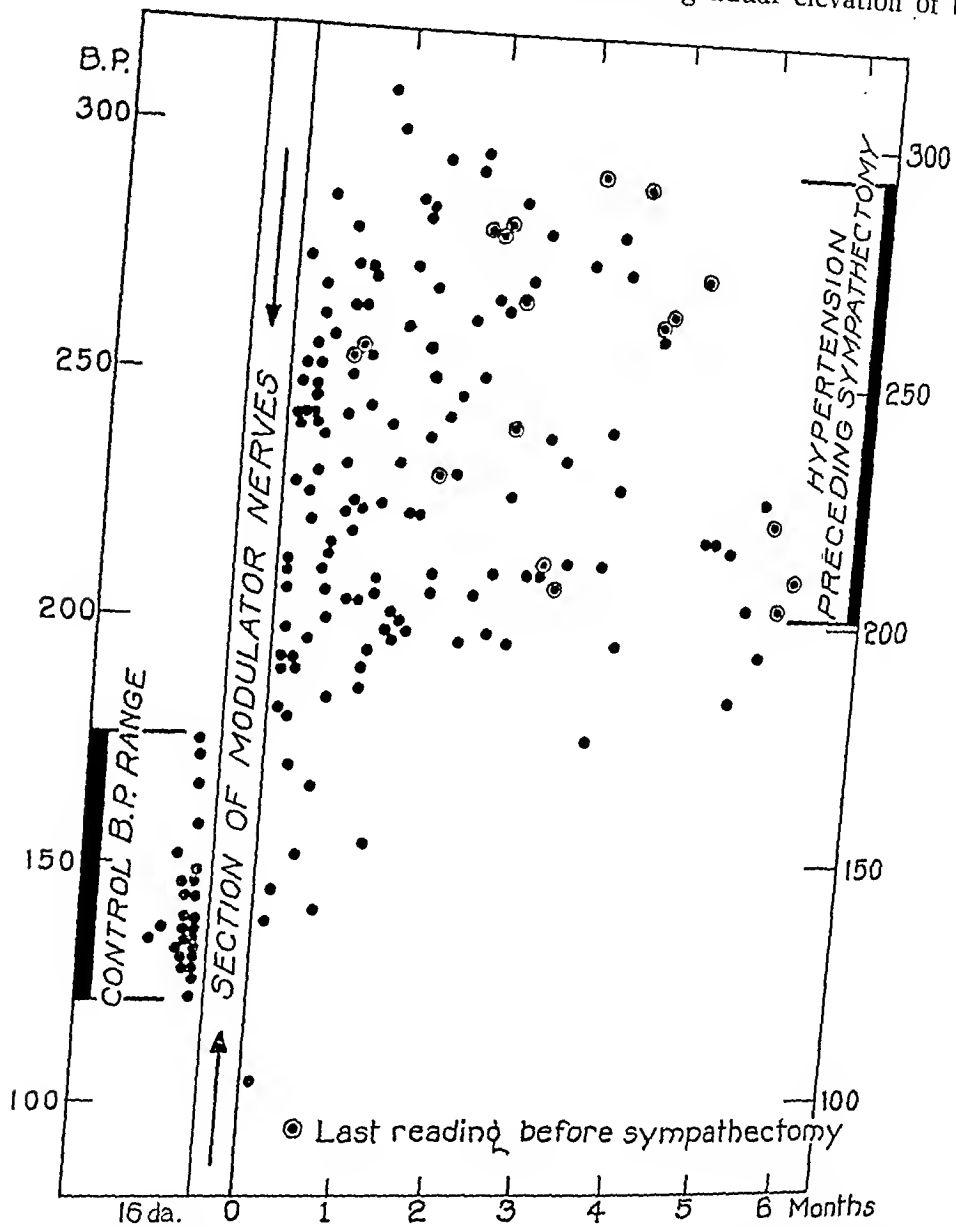


Chart 1.—Blood pressure reading for 18 dogs before and after excision of both carotid sinuses and division of the entire vagus-sympathetic-depressor nerve in one side, and the sympathetic depressor nerves in the other side, of the neck.

pressure; the value reached 202 mm. in forty-two days and then receded to the preoperative level at seventy-four days. The remaining vagus trunk was then explored, and its entire medial half was divided. This failed to elevate the blood pressure appreciably. One hundred and forty-

six days after the operation the dog was anesthetized with chloralose (chloral hydrate and dextrose) and the remaining portion of the right vagus nerve was divided. During the succeeding half-hour of observation no elevation of the blood pressure occurred. This animal, in spite of occasional vomiting, had maintained its body weight fairly well, and it is difficult to explain the failure of development on enduring hypertension. None of these 24 dogs at any time showed symptoms of post-mortem appearances consistent with the malignant phase of hypertension.

Neurogenic Hypertension, Renal Denervation and Total Paravertebral Sympathectomy.—Cannon, Newton, Bright, Menkin and Moore⁶⁴ showed in cats and later in dogs that complete removal of the paravertebral sympathetic chains is compatible with life. In this laboratory 54 dogs have been sympathectomized by a modification of the Cannon technic, previously reported.⁶⁵ Blood pressures were observed in 36 instances. Some of these animals have been observed as long as three years and five months. Their behavior and activity are practically normal. The effect of treatment of experimental neurogenic hypertension by total paravertebral sympathectomy was studied in 3 of the 18 hypertensive dogs previously described. The kidneys in 2 of these dogs had previously been denervated at their pedicles, in 1 before and in 1 after division of the modulator nerves. This did not appear to alter the elevation of blood pressure that followed division of the modulator nerves. The effect of complete sympathectomy on the blood pressure of these 2 dogs is shown in chart 2. In a third dog, an old animal, the kidneys were not denervated. Its blood pressure averaged 174 mm. of mercury before section of the modulator nerves, 226 mm. of mercury during eighty-three days of neurogenic hypertension and 123 mm. of mercury during twenty-four days of observation after completion of the total sympathectomy.

Paravertebral Sympathectomy Followed by Section of the Modulator Nerves.—In 8 dogs the aforementioned procedure was reversed by first performing complete paravertebral sympathectomy and later sectioning the modulator nerves. In normal dogs the blood pressure is moderately lowered by complete paravertebral sympathectomy, but within one to three months it begins to rise, and within six to twelve months it returns to preoperative levels. Accompanying this there is partial restoration

64. Cannon, W. B.; Newton, H. F.; Bright, E. M.; Menkin, V., and Moore, R. M.: Some Aspects of the Physiology of Animals Surviving Complete Exclusion of the Sympathetic Nerve Impulses, *Am. J. Physiol.* **89**:84, 1929.

65. (a) Wilson, H.; Roome, N. W., and Grimson, K.: Complete Sympathectomy, *Ann. Surg.* **103**:498, 1936. (b) Grimson, K. S.; Wilson, H., and Phemister, D. B.: The Early and Remote Effects of Total and Partial Paravertebral Sympathectomy on Blood Pressure, *ibid.* **106**:801, 1937.

of central vasopressor control.^{65b} To avoid this period of blood pressure recovery, the operations on the carotid sinuses and the depressor nerves were performed either within a month of completion of the sympathectomy or more than a year later, at which time the preoperative blood pressure had been restored.

Section of the Modulator Nerves Before Recovery: Six dogs were completely sympathectomized in three stages and then subjected to section of the modulator nerves within a month. All tolerated the section poorly. The first 2 died: 1, after six hours, with symptoms suggesting decerebrate rigidity, and the other, after twenty-four hours, with vasomotor collapse. The other 4 were given fluids intravenously each day

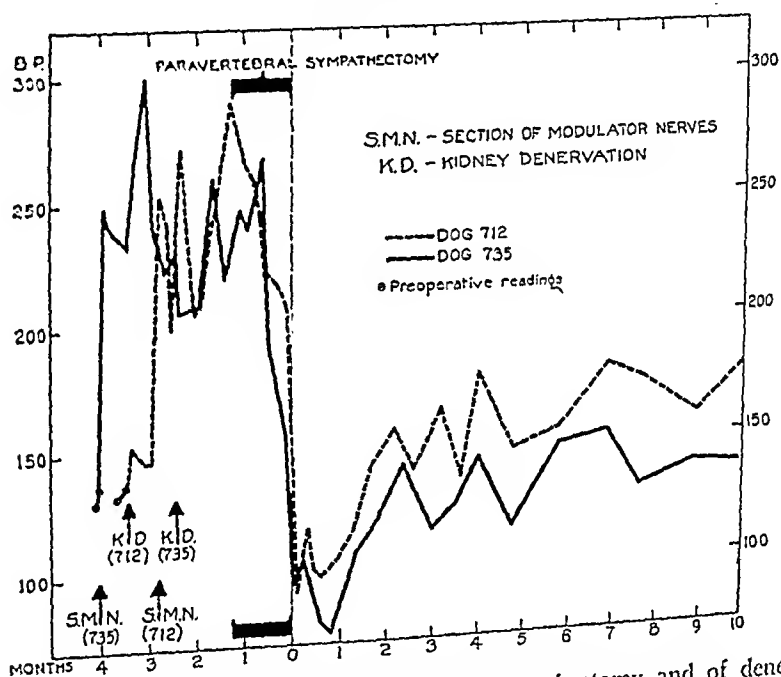


Chart 2.—Effect of complete paravertebral sympathectomy and of denervation of the kidney on neurogenic hypertension produced by section of the modulator nerves.

and after a week were in good condition. One of these, which almost died, was given an intracardiac injection of epinephrine hydrochloride at the time of the operation. The blood pressures of these 4 dogs averaged 144 mm. of mercury before the sympathectomy and 107 mm. of mercury during the periods of fourteen to twenty-eight days that preceded section of the modulator nerves. They were eating well and in good general condition when this procedure was carried out. During the following month their blood pressures averaged 101 mm. of mercury. The highest single reading observed was 146 mm. (on the twenty-eighth postoperative day). One of these dogs was observed three hundred and ten days after section of the modulator nerves. The blood pressure

gradually rose until, during the last three months, it averaged 222. The blood pressure elevation beginning a month after section of the modulator nerves and the indifferent effect of celiac ganglionectomy in the other dog (dog 678) are shown in chart 3.

Section of the Modulator Nerves After Recovery: Two dogs with control blood pressures averaging 148 and 146 mm. of mercury respectively were sympathectomized. During the first three months after sympathectomy their blood pressures averaged 134 and 110 mm. of mercury respectively. In seven and eleven months respectively they had regained their preoperative levels. During the next sixteen and seventeen months their blood pressures averaged 149 and 152. At this time the modulator nerves were divided. During the following thirty-one days their pressures averaged 173 and 165 mm. of mercury respectively.

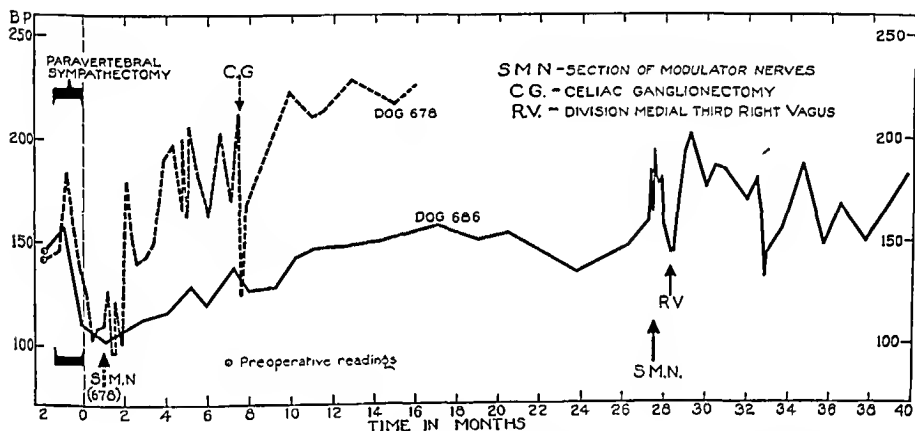


Chart 3.—Blood pressure changes following total paravertebral sympathectomy and subsequent section of the modulator nerves. Section was performed before the period of vasomotor recovery that ordinarily follows complete sympathectomy in dog 678 and after this period in dog 686. Note that several months elapsed between section of the modulator nerves and the development of definite hypertension in dog 678.

At this time their necks were reoperated on, and in each the medial third of the remaining portion of the vagus nerve was cut. They have since been observed for one hundred and seventy-eight days and have had average blood pressures of 159 and 165 mm. of mercury respectively. The blood pressure curve for the second of these 2 dogs (dog 686) is shown in chart 3.

Neurogenic Hypertension, Section of Splanchnic Nerves and Abdominal Sympathectomy.—The effect of subdiaphragmatic resection of the splanchnic nerves on experimental neurogenic hypertension was studied in 4 dogs. The modulator nerves were divided, and then, when

the blood pressure elevation seemed stabilized, the abdomen was opened through a midline incision, the abdominal sympathetic chains were removed and all of the splanchnic nerves were divided where they pass through the crux of the diaphragm. The effect on the blood pressure is shown in table 1.

Neurogenic Hypertension, Section of Splanchnic Nerves, Abdominal Sympathectomy and Celiac Ganglionectomy.—In 4 dogs the procedure just described was repeated, except that in addition to removal of the abdominal sympathetic chains and division of the splanchnic nerves at the diaphragm, the celiac ganglion was excised as completely as possible. The effect on all 4 dogs is shown in table 2 and in the graph of dog 701 in chart 4.

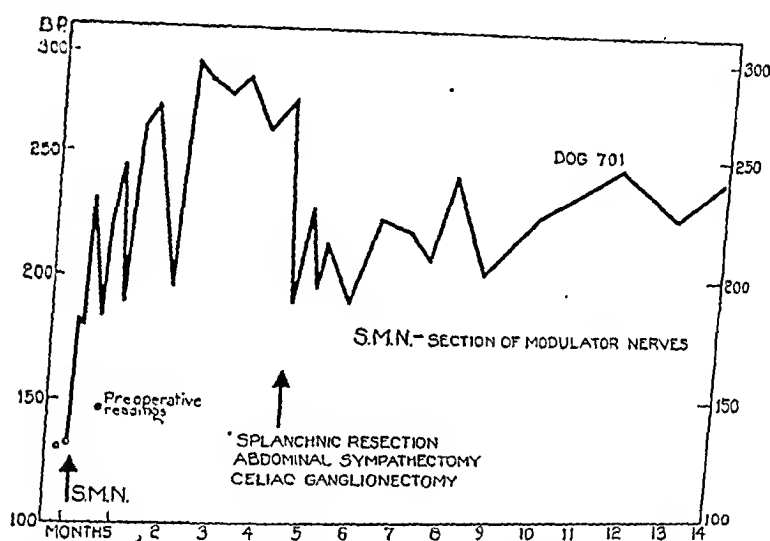


Chart 4.—Effect on blood pressure of subdiaphragmatic resection of the splanchnic nerves, abdominal sympathectomy and celiac ganglionectomy in dog 701. This operation was performed five months after section of the modulator nerves and the associated development of neurogenic hypertension.

In 3 dogs the lower six thoracic and first lumbar sympathetic ganglions were removed, together with several centimeters of the splanchnic nerve, through bilateral transthoracic approaches after resection of portions of the tenth rib. Both sides were treated at one operation. Table 3 shows the effect of this procedure on blood pressure.

Neurogenic Hypertension and Bilateral Excision of Upper Six Thoracic Ganglions.—In 2 dogs the upper six thoracic ganglions were removed at one operation through bilateral transthoracic approaches after resection of segments of the fourth rib on either side. The control blood pressures were 128 and 158 mm. of mercury, and the average blood pressures were 261 and 257 mm. of mercury, during the sixty-two days of observation following section of the modulator nerves. Fifty-seven

days after bilateral removal of the upper six thoracic sympathetic chains the blood pressures were 218 and 220 mm. of mercury respectively. The pulse rates have averaged 98 and 118 respectively since this operation.

Neurogenic Reflex "Renal" Hypertension.—It has been established in the literature and in the studies reported that experimental neurogenic hypertension following section of the modulator nerves is neither

TABLE 1.—*Effect of Subdiaphragmatic Resection of Splanchnic Nerves and Removal of Abdominal Sympathetic Chains*

Dog	Control Blood Pressure	Average Neurogenic Hypertensive Pressure	Blood Pressure After Resection of Splanchnic Nerves and Abdominal Sympathectomy									
			1 Mo.	2 Mo.	3 Mo.	4 Mo.	5 Mo.	6 Mo.	7 Mo.	8 Mo.	9 mo.	10 Mo.
139	126	70 days, 257	192	104	216	206	216	276	284
23	138	75 days, 256	150	172	200	218	200	198	202	174	200	196
137	122	122 days, 264	209	222	266	220	232	...	284
10	148	85 days, 215	218	196	170	172	152	151	170	212

TABLE 2.—*Effect of More Extensive Procedure*

Dog	Control Blood Pressure	Average Neurogenic Hypertensive Pressure	Blood Pressure After Resection of Splanchnic Nerves, Abdominal Sympathectomy and Celiac Ganglionectomy										
			1 Mo.	2 Mo.	3 Mo.	4 Mo.	5 Mo.	6 Mo.	7 Mo.	8 Mo.	9 Mo.	10 Mo.	11 Mo.
96	144	16 days, 258	257	263	283	322	297	301	...	300	318	256	304
701	131	130 days, 238	207	206	214	242	202	226	242	...	226	240	220
133	136	112 days, 286	235	246	266	264	272	258	294	...	234
22	134	79 days, 212	170	158	160	217	210	236	222	226	192	...	220

TABLE 3.—*Effect of Bilateral Low Thoracic Sympathectomy and Resection of Splanchnic Nerves*

Dog	Preoperative Control Blood Pressure	Average Neurogenic Hypertensive Pressure	Blood Pressure After Bilateral Lower Thoracic Sympathectomy and Resection of Splanchnic Nerves				
			1 Mo.	2 Mo.	3 Mo.	4 Mo.	5 Mo.
50	128	175 days, 195	181	212	228	214	222
101	136	161 days, 202	204	206	242	212	206
49	132	161 days, 219	209	170	214	226	246

Dog 49 required reoperation and division of the medial third of the remaining right vagus nerve before the neurogenic hypertension became established. The blood pressure average and time under "Neurogenic Hypertension" are after the second operation on the neck.

prevented nor appreciably altered by renal denervation. The following experiment was designed to determine whether the converse held true, i. e., whether hypertension could be effected after sympathetic denervation of everything except the kidneys. Total sympathectomy was performed except for the nerve supply to the adrenals and kidneys, and then the modulator nerves were sectioned. This was done to see whether the reflex sympathetic stimulation of these organs only would result in hypertension. Section of the modulator nerves, as is confirmed by the foregoing experiments, does not effect an immediate elevation of blood

pressure in totally sympathectomized dogs. The delayed elevation of blood pressure previously described and illustrated in chart 3 (dog 678) did not develop sooner than six weeks after completion of the sympathectomy, a month after section of the modulator nerves. Its progression to a sustained, moderately hypertensive level was gradual, requiring at least four months.

The technic of total sympathectomy except for the sympathetic outflow to the kidneys and the adrenal glands, together with the early results of section of the modulator nerves on 3 dogs and of subsequent renal denervation of 2 of them, has been previously reported from Professor Heymans' laboratory in a preliminary form by Bouckaert and Heymans and me.⁶² This type of sympathectomy is performed in three stages. In the first stage the abdominal sympathetic chains below the

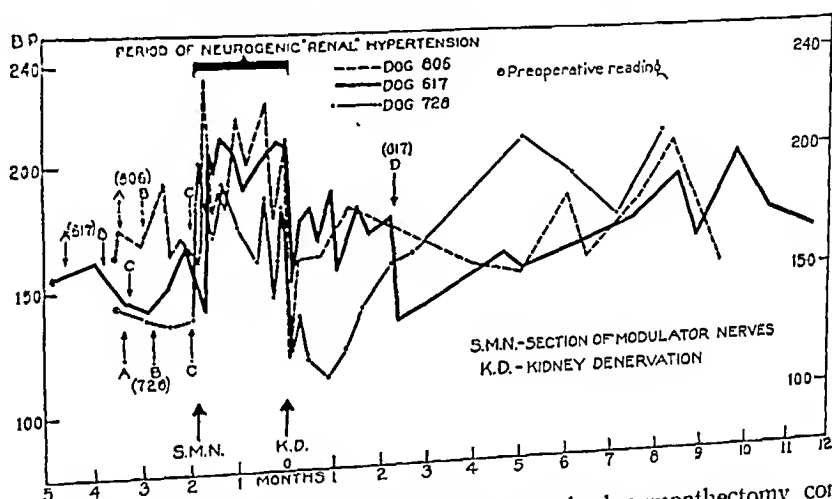


Chart 5.—Effect on blood pressure of paravertebral sympathectomy complete except for the splanchnic nerve supply to the adrenals and kidneys and of subsequent section of the modulator nerves and renal denervation. *A*, *B* and *C*, three stages of sympathectomy, which was total except for the splanchnic nerve supply to the adrenals and the kidneys. *S*, *M*, *N*, section of the modulator nerves. *K*, *D*, denervation of the kidneys at their pedicles. *C*, subsequent section of the splanchnic nerves in dog 617.

second lumbar ganglion are removed; the first and second lumbar somatic nerves are cut distal to the origin of the sympathetic rami, and the branches of the celiac and superior mesenteric ganglions are divided, only those running to the kidneys being left. The second and third operations consist of the removal from first one and then the other side of the chest of the first seven thoracic sympathetic ganglions, including the stellate ganglion, and division of the lower six intercostal nerves just distal to the origin of the sympathetic rami. This procedure when properly executed should leave the animal completely sympathectomized except for the origin and course of the splanchnic nerves through the diaphragm passing near the adrenal glands and through the celiac and

TABLE 4.—*Effect of Renal Denervation and Section of Modulator Nerves*

Dog	Control Blood Pressure	Blood Pressure After Three Stage Operation	After Section of Modulator Nerves									After Renal Denervation																				
			1			2			3			4			5			6			7			9			10			11		
			Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Wk.	Mo.	Mo.	Mo.	Mo.	Mo.	Mo.	Mo.	Mo.	Mo.	Mo.	Mo.	Mo.		
Gent 1.....	132	23 days, 128	167	125	226	226			
590.....	116	11 days, 132	208		
Gent 2.....	115	26 days, 101	170	161	157	152	159		
Gent 3.....	109	57 days, 131	127	150	181	180	188	203	191		
728.....	111	16 days, 138	190	178	192	174	...	160	186	153	180	132	132	145		
617.....	156	32 days, 152	200	210	203	190	200	...	208	206	...	152	175	171	172	178*	144	...	157	162	172	179		
801.....	169	12 days, 161	207	188-	182	218	200	222	178	208	..	160	...	162	...	180	...	158	151	170	180	201	152	186	172		

* Subdiaphragmatic section of splanchnic nerves and excision of remaining lumbar ganglions.

superior mesenteric ganglions to the kidneys. Section of the modulator nerves should then influence only the adrenal glands and the kidneys.

Nine dogs have been prepared in this manner, including those operated on in Ghent. Seven of these underwent section of the modulator nerves. All 7 showed moderate but definite hypertension. Studies of the pulse rates of 3 of these dogs showed no definite acceleration. Since the hypertension might be explained by overlooked sympathetic branches, increased secretion of epinephrine or a renal influence, the effect of denervation of the kidneys at their pedicles was studied in 5 of these dogs. This renal denervation substantially reduced the hypertension in each instance. Table 4 summarizes the results.

Blood pressure graphs of 2 of these dogs (Ghent 1 and Ghent 2) are reproduced (Heymans and Bouckaert⁶⁶). The data on the remaining 3 which subsequently underwent renal denervation are graphed in chart 5. It is of interest that recovery of the blood pressure in these almost completely sympathectomized dogs was observed months after renal denervation. This parallels the phenomenon previously described as occurring in totally sympathectomized dogs.

This experiment suggests that there may be some correlation between experimental neurogenic hypertension and renal hypertension. In this respect a consideration of possible humoral factors is important. Heymans and Bouckaert,⁶⁷ in a preliminary report, stated that the blood of neurogenic hypertensive animals produces more vasoconstriction of a test spleen than does the blood of normal animals. Goormaghtigh has observed changes in cells of the media of the arterioles of the juxtaglomerular apparatus in kidneys of neurogenically hypertensive animals which resemble those seen in the kidneys of animals with renal hypertension produced by obstruction of the renal arteries.

Interpretation of these reports is difficult. It is, however, of interest that experimental neurogenic hypertension does not seem to be dependent on sympathetic innervation of the splanchnic area, kidneys or adrenals. The highest blood pressure observed in our laboratory, 322 mm. of mercury, was observed in an animal (dog 96) after section of the modulator nerves and subsequent abdominal sympathectomy and division of the splanchnic nerves. The completeness of the abdominal sympathectomy has been checked by a subsequent exploratory operation.

SUMMARY

Surgical efforts to treat clinical hypertension in certain instances by denervation of the splanchnic area and the clinical emphasis placed on

66. Heymans, C., and Bouckaert, J. J.: *Au sujet de l'hypertension artérielle expérimentale*, Bull. Acad. roy. de méd. de Belgique 4:441, 1939.

67. Heymans, C., and Bouckaert, J. J.: *Vasoconstrictor Properties in Blood of Hypertensive Dogs*, Proc. Soc. Exper. Biol. & Med. 39:94, 1938.

psychosomatic factors and vasomotor instability in many patients with "essential hypertension" have stimulated this study of the role of the sympathetic nervous system in the neurogenic type of hypertension produced in dogs by the disturbance of vasomotor regulation following section of the modulator, buffer or depressor nerves.

The existence of this hypertension has been confirmed by its production in 18 normal dogs. Ten had mean systolic blood pressures ranging from 250 to 300, and 8 had pressures ranging from 200 to 250, mm. of mercury. Complete removal of the paravertebral sympathetic chains prevented the elevation of blood pressure that ordinarily follows section of the modulator nerves provided that these nerves are cut before the onset of the incomplete vasomotor recovery which ordinarily follows complete sympathectomy in dogs. Similarly, total paravertebral sympathectomy reduced the blood pressure of neurogenic hypertensive animals to or below normal for a time (four to six weeks). During and after the phase of vasomotor and blood pressure recovery that follows total sympathectomy these two groups of dogs had elevations of the blood pressure above normal.

The effect of (*a*) renal denervation, (*b*) division of the splanchnic nerves and abdominal sympathectomy, (*c*) division of the splanchnic nerves, abdominal sympathectomy and celiac ganglionectomy, (*d*) lower thoracic sympathectomy and section of the splanchnic nerves and (*e*) upper thoracic sympathectomy on the blood pressures of neurogenic hypertensive dogs was studied. Hypertension was observed after each of these procedures.

Hypertension, apparently of renal origin, was observed to follow division of the modulator nerves in dogs completely sympathectomized except for the splanchnic nerve distribution to the adrenal glands and kidneys. This was markedly reduced by subsequent denervation of the kidneys. Late elevations of pressure, apparently parallel to those observed in totally sympathectomized dogs, were seen in some of these animals.

COMMENT

It is always difficult to estimate the value of experimental studies in attempting evaluations of clinical problems. Many authors have, however, spoken of renal types and of neurogenic types of clinical hypertension. A form of experimental hypertension similar in many respects to each of these two types of clinical hypertension can be produced in dogs. The renal type may be produced by a Goldblatt clamp or by Page⁶⁸ perinephritis, and the neurogenic type, by removal of the regulating influence of the modulator nerves.

68. Page, I. H.: The Production of Persistent Arterial Hypertension by Cellophane Perinephritis, *J. A. M. A.* **113**:2046 (Dec. 2) 1939.

The experimental renal type of hypertension, in my experience and in that of others, develops a somewhat more modest blood pressure elevation. The malignant phase of hypertension is seen with this type, at times without great elevation of blood pressure. The neurogenic type of experimental hypertension seems to develop greater elevations of blood pressure, but not once has a malignant type of hypertension been observed. This would seem to indicate that the malignant phase of experimental hypertension may be a renal phenomenon. If a parallel exists in clinical hypertension, one might postulate that the malignant phase occasionally seen in patients with essential, or idiopathic, hypertension is also a renal phenomenon.

Many laboratory and clinical studies would seem to indicate that little benefit can be obtained in cases of "renal" hypertension by denervation of the kidney done either directly or through denervation of the splanchnic area. Laboratory tests by many investigators of the effect of denervation of the splanchnic area on dogs with renal hypertension would indicate that little symptomatic lowering of the blood pressure can be achieved.

As has been stated, many authors have referred to neurogenic types of clinical hypertension or have emphasized the importance of neurogenic elements in many patients with hypertension of the essential, or idiopathic, type. These central vasopressor influences must, according to present physiologic concepts, be reflex and expressed through the vasomotor center and over the sympathetic nervous system. If clinical hypertension primarily of this type exists, it may in many respects resemble the neurogenic hypertension produced in dogs by sectioning the modulator nerves and thus removing their buffering influence against reflex vasopressor stimuli reaching the vasomotor center. The experiments cited have emphasized that it is in cases of this type of hypertension that the greatest benefit may be expected from surgical intervention directed toward the sympathetic nervous system. The observation of incomplete central vasomotor recovery following total sympathectomy has placed some limitation on the duration of the benefits that may be expected from such intervention. Another limitation is offered by the presence of irreversible pathologic changes of blood vessels, which can maintain a fixed increased peripheral resistance, independent of nervous or humoral influences.

The experiments dealing with neurogenic hypertension have given some indication of what may be expected from various types of sympathetic denervation. The importance of the splanchnic area seems to have been overemphasized. Denervation of the splanchnic area in these experiments lowered the blood pressure only slightly or not at all. This corresponds to the previously reported observations that denervation of the splanchnic area of various types does not appreciably alter the vaso-

pressor response to increased intracranial pressure. Total sympathectomy, on the other hand, prevents it.^{65b} These observations have been confirmed and elaborated by Freeman and Jeffers,⁶⁹ who have suggested that sympathetic denervation of both the heart and the adrenal glands will also prevent the elevation of blood pressure produced by increased intracranial pressure. It must be remembered that as the humoral aspect of hypertension is worked out it may be found that any large vascular bed may be under a humoral vasoconstrictor control quite independent of its own sympathetic innervation.

In a previous report ^{65b} it was demonstrated that total sympathectomy prevents the pressor response to increased intracranial pressure. The foregoing experiments have shown that total sympathectomy also prevents or abolishes for a time the elevation of blood pressure that follows section of the modulator nerves. Various types of localized sympathetic denervation have not prevented either of these types of neurogenic hypertension. It therefore seems likely that better results may be expected from total sympathectomy than from partial sympathectomy directed toward localized vascular beds, such as the splanchnic area.

69. Freeman, N. E., and Jeffers, W. A.: Effect of Progressive Sympathectomy on Hypertension Produced by Increased Intracranial Pressure, *Am. J. Physiol.* **128**:662, 1940.

REVIEW OF UROLOGIC SURGERY

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(Concluded from page 167)

RENAL RICKETS

Charnock⁵² stated that renal rickets is a disease of childhood in which chronic renal insufficiency is associated with osseous changes closely resembling those of late rickets. The clinical picture is that of a stunted, deformed child suffering from diminished renal function, severe acidosis and altered calcium-phosphorus metabolism.

The renal lesions present a wide variety of conditions with reduction in functioning tissue the predominating picture.

The bone changes affect principally the regions of the growth disks, with a general tendency to osteoporosis. The picture is one of calcium deficiency.

Three etiologic theories are discussed: 1. The renal theory, which supposes that the waste phosphates ordinarily found in the urine may be excreted into the intestines and that these can interfere with the absorption of calcium by the formation of insoluble calcium phosphates. 2. The theory that parathyroid hypertrophy is compensatory to the high level of blood phosphorus and thus is secondary to the renal disease. 3. The

52. Charnock, D. A.: Renal Rickets, *J. Urol.* **44**:850-859 (Dec.) 1940.

theory of pituitary-diencephalic lesion. This would explain the entire clinical picture. It is suggested that an overlap of all these theories may eventually clear the etiologic difficulties.

Treatment consists of combating the severe acidosis and relief of urinary obstruction.

HYPERTENSION

Crabtree and Chaset⁵³ studied 150 approximately consecutive cases in which nephrectomy was performed. The conditions were representative of severe unilateral renal damage. Hypertension was not common in the clinical picture in this group. Vascular changes, which have been considered causes of hypertension, were present in a high percentage of the cases. Elevation of blood pressure was not the rule, even with chronic pyelonephritis, in these cases. Nephrectomy was not followed by appreciable reduction in blood pressure readings before operation. The exact cause of renal (ischemic) hypertension is as yet unknown. The pathologic and anatomic elements seem less important than a physiologic element as yet unknown. Evidence was not produced by this study to encourage employment of nephrectomy in cases of hypertension except for recognized surgical indications.

Braasch, Walters and Hammer⁵⁴ stated that the incidence of hypertension in a group of 1,684 patients subjected to renal surgical operation was no higher than in a group of patients taken at random. In a study of the incidence of hypertension the factor of age is important.

The renal lesion amenable to surgical treatment which occurs most often in association with hypertension is atrophic pyelonephritis. Hypertension afflicted 20 of 43 patients operated on for primary atrophic pyelonephritis, or 46.5 per cent. The incidence of hypertension is low in cases in which operation is performed for pyelonephritis without atrophy and sclerosis. Acute infection of the renal cortex or perinephric abscess is seldom a factor in causing hypertension.

Hypertension was observed in 161 cases, or 20.3 per cent, of 793 cases in which operation was performed for renal stone. The role of secondary infection is important, since hypertension occurred in 22.5 per cent of cases in which infection was manifest and in only 5.7 per cent of cases in which there was no infection. However, the deciding factor was not the degree of infection but the presence of extensive vascular sclerosis and parenchymal atrophy.

53. Crabtree, E. G., and Chaset, N.: Vascular Nephritis and Hypertension: A Combined Clinical and Clinicopathologic Study of One Hundred and Fifty Nephrectomized Patients, *J. A. M. A.* **115**:1842-1846 (Nov. 30) 1940.

54. Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, *J. A. M. A.* **115**:1837-1841 (Nov. 30) 1940.

Hypertension was noted in approximately 14 per cent of cases of hydronephrosis without stone for which operation was performed.

Hypertension was found in 38, or 27.7 per cent, of 137 cases in which operation was performed for renal adenocarcinoma. The comparatively high incidence of hypertension in this group of cases was increased by the factor of age, since 87 patients, or 63.5 per cent, were in the sixth decade of life or older. The exact influence of the neoplasm is obscure; the secretion of a pressor substance has been surmised, but corroboratory chemical and physiologic evidence is wanting.

Hypertension may develop in a variable time after a previous conservative renal operation. In many cases the blood pressure becomes normal after removal of the affected kidney. In every case of hypertension in which there is a history of previous operation the possibility of postoperative nephrosclerosis must be considered.

Renal insufficiency apparently is not a factor in causing hypertension.

Back pressure resulting from renal stasis usually is not a factor in hypertension unless acute bilateral obstruction is present.

A follow-up study was made in 198 cases in which hypertension was present and in which surgical operation was performed. The blood pressure became normal after operation in 65, or a third, of the cases and remained normal for a year or more.

It may be predicated that hypertension will be relieved by surgical operation in approximately 70 per cent of cases in which it accompanies atrophic pyelonephritis, in 50 per cent of cases in which it is associated with renal tuberculosis and in 25 per cent of cases in which it is an accompaniment of renal stone, hydronephrosis or tumor.

Although hypertension associated with surgical lesions of the kidney is more often relieved by nephrectomy than by conservative operation, the blood pressure often returned to normal after nephrolithotomy and renal drainage.

Reduction in blood pressure may exist as long as a year or more after operation, and yet hypertension may return. This may be explained on the ground that a toxic or irritant lesion has been eliminated; when the influence of such a lesion has worn off, the underlying essential hypertension reasserts itself.

Braasch and Jacobson,⁵⁵ in an analysis of 180 cases of chronic bilateral pyelonephritis, found an incidence of hypertension of 26.1 per cent, or an increase of 6 per cent over that found in their control group of cases. This increase was particularly prominent among patients with pyelonephritis who were less than 50 years of age; among these patients the incidence of hypertension was found to be almost twice that noted

55. Braasch, W. F., and Jacobson, C. E.: Chronic Bilateral Pyelonephritis and Hypertension, *J. Urol.* 44:571-579 (Nov.) 1940.

in the control group. The incidence of hypertension among the patients 50 years or more of age was found to be approximately the same in the two groups.

An apparent relation was found to exist between the incidence of hypertension and the duration of symptoms of pyelonephritis. Although in most cases the incidence of hypertension increased with the duration of symptoms, there were some cases in which the blood pressure remained normal after the pyelonephritis had existed for from fifteen to twenty years.

Apparently there is also a relation between the degree of pathologic change in the kidneys and ureters as evidenced by the degree of deformity in the urogram and the incidence of hypertension. The highest incidence occurs in those cases in which the pathologic changes are most marked.

Impaired renal function does not necessarily imply the presence of hypertension. In fact, the blood pressure was normal in more than half of the cases in which impaired renal function was noted. However, hypertension was found twice as often in cases of impaired renal function as in those of normal renal function.

In approximately 75 per cent of the cases of hypertension the systolic blood pressure was less than 180 mm. of mercury, and in only 4 cases was the systolic blood pressure more than 200 mm. of mercury. Thus, though it appears that pyelonephritis contributes to the incidence of hypertension, the hypertension occurring in these cases is usually comparatively benign.

Hypertension is occasionally observed in cases of mild or recurrent chronic pyelonephritis in which renal function is normal and there is no urographic deformity. From various clinical data, the hypertension appears to be of independent origin and may be termed "essential hypertension."

Schroeder and Fish⁵⁶ performed nephrectomy on 7 patients exhibiting arterial hypertension associated with organic renal disease. Two were markedly improved and 2 slightly improved, but all had remained actually or potentially hypertensive. This form of therapy may prove of benefit, but, it seems, only in cases in which the existence of hypertension is of short duration and in which arteriolar sclerosis of the other kidney is not advanced. Its use is limited, therefore, to a small number of cases.

Schroeder and Fish suggested the following criteria for selection of cases suitable for this form of therapy:

The onset of arterial hypertension should be known to have occurred recently. These authors placed the time arbitrarily at two years.

56. Schroeder, H. A., and Fish, G. W.: Studies on "Essential" Hypertension: III. The Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, *Am. J. M. Sc.* **199**:601-616 (May) 1940.

The renal lesion should be confined to one kidney and should be such that diminution of function has occurred in that kidney.

Renal function, as measured by the ability of both kidneys to concentrate urine and by the urea clearance test, should be within normal limits.

Retinitis should be absent and changes in the caliber of the vessels of the retina minimal.

Arterial pressure should be persistently elevated.

These criteria were followed in only 1 case; in the others the patients had exhibited bilateral disease, hypertension of long duration or some diminution of renal function. Unless suitable cases are selected, many kidneys may be removed needlessly and without benefit. This experience has served to suggest that when long-standing hypertension is present or when a so-called malignant course has commenced this form of therapy is not wise.

Dicker,⁵⁷ in discussing the reports of 2 cases, stated that only kidneys with restricted circulation can cause hypertension; all the other renal and urinary manifestations are secondary, independent and incapable of playing a part in the production and maintenance of hypertension.

Campbell⁵⁸ reviewed the records in 173 cases to determine the value of gradual decompression of the bladder. He reached the following conclusions:

Gradual decompression is still a valuable procedure and is often life saving for the patient with prostatic disease who has chronic urinary retention with a systolic blood pressure of 160 mm. or more.

Blood pressure is reliable as a guide to determine the necessity for decompression.

Pyelonephritis, often pointed to as the actual cause of death, is undoubtedly a secondary complication precipitated by the too rapid evacuation of a chronically distended and infected bladder.

Decompression is an invaluable procedure, indicated in a small group of cases not only to carry the patients through the initial crisis but to prepare them more adequately for operative procedures and their period of convalescence.

A theory is advanced that hypertension occurs among a small group of patients with prostatic disease because of inability of the upper part of the urinary tract to dilate, due to an anatomic factor, namely, an intra-renal pelvis.

57. Dicker, E.: The Rôle of the Kidney in the Pathogenesis of Arterial Hypertension, *Am. J. M. Sc.* **199**:616-621 (May) 1940.

58. Campbell, E. W.: The Significance of Hypertension in Prostatics with Chronic Urinary Retention, *J. Urol.* **45**:70-81 (Jan.) 1941.

Boyd,⁵⁹ in discussing Campbell's article on the significance of hypertension in prostatics with chronic urinary retention, stated that he had seen 2 patients who had become seriously ill after sudden decompression and 1 patient who had died. In the 3 cases, of the patient who died and of the 2 patients whose bladders were inadvertently emptied of a large quantity of chronically retained urine, the bladders looked like purple velvet, edematous and ecchymotic.

Chronic obstruction of the vesical neck is associated with thickening of the bladder and narrowing of the portion of the ureter as it passes through the bladder wall; then dilatation of the lower portion of the ureter, followed by ascending dilatation of the ureter, then of the kidney pelvis and finally of the calices. The result is impairment of renal function due to arterial changes in the cortex of the kidney resulting from hydronephrosis, as Hinman has clearly demonstrated in his work on hydronephrosis.

ANEURYSM OF THE ABDOMINAL AORTA SIMULATING UROLOGIC DISEASE

Uhle⁶⁰ discussed the etiology, pathogenesis and symptomatology of aneurysms of the abdominal aorta masquerading as primary urologic entities. The fundamental consideration of the history and physical examination is important and has been overlooked too often in cases in which aneurysm of the abdominal aorta simulates acute urologic crisis. Conditions simulating perinephritic abscess, renal lithiasis, hydronephrosis, renal tumor and perirenal hemorrhage from trauma have been cited.

The abnormalities noted on physical examination require confirmation or additional diagnostic aid from cystoscopic and roentgen ray examinations. Erosion of the vertebral bodies should be searched for in every case in which the presence of aneurysm of the abdominal aorta is suspected. The importance of a lateral or a lateral-oblique roentgen view is emphasized. Exploratory operations in the absence of adequate study are to be condemned.

Wesson,⁶¹ in discussing Uhle's and Howard, Suby and Harberson's articles on aneurysm, stated that before the day of the germ theory trauma was considered the cause of aneurysm, as it was the universal etiologic agent. Now it is recognized by practically all scientists that aneurysms are due to *Spirochaëta pallida* or to streptococci, and when-

59. Boyd, M. L., in discussion on papers of Campbell,⁵⁸ Peirson and Wilson and Kickham,⁵⁶ *J. Urol.* 45:102-105 (Jan.) 1941.

60. Uhle, C. A. W.: The Significance of Aneurysm of the Abdominal Aorta Masquerading as Primary Urologic Disease, *J. Urol.* 45:13-40 (Jan.) 1941.

61. Wesson, M. B., in discussion on papers of Uhle,⁶⁰ Howard, Suby and Harberson¹⁷ and Prather, *J. Urol.* 45:65-67 (Jan.) 1941.

ever trauma is mentioned prominently as the cause of any disease it is as well to be honest and to realize that the field of scientific discussion has been left and that the field of financial medicine has been entered.

Wesson found only 35 cases of true renal aneurysm reported, and in 9 of these the diagnosis had been made preoperatively. The term "false aneurysm" is misleading. The diagnosis should be expressed as a traumatic or spontaneous rupture of the kidney or artery with anatomic control of bleeding.

Hematoma is a sign of various diseases of the blood vessels in the kidney substance, and is never due to aneurysm unless there is a rupture into the pelvis.

When calcified aneurysmal dilatations are present they appear as signet ringlike shadows, which are quite dense. Small sections of the circumference are frequently invisible and usually represent the sites of junction of the lumens of the afferent and efferent parts of the vessel with that of the aneurysm. Since true aneurysms are practically always symptomless, the diagnoses have been made incidentally in the course of renal investigation.

GLANDULAR THERAPY

Pool, Cook and Kepler⁶² discussed the treatment of cryptorchidism, impotence and prostatic obstruction with (1) chorionic gonadotropin (A. P. L. was used), (2) extracts of the anterior lobe of the pituitary body, (3) pregnant mare's serum and (4) testosterone propionate.

These authors recommended intramuscular injections of chorionic gonadotropin in doses varying from 200 to 500 rat units once or twice weekly. This should be continued for from two to six months. They expressed the belief that the indications for the use of chorionic gonadotropin in cases of cryptorchidism have not been established definitely and that cures have been attributed to glandular therapy when actually the patients never had cryptorchidism.

They pointed out a serious objection to the use of testosterone propionate in that the compound tends to inhibit spermatogenesis.

The etiology of impotence was discussed and tabes dorsalis, multiple sclerosis, transverse myelitis and lead poisoning were offered as examples of impotence on the basis of pathologic conditions that interfere with the afferent and efferent fibers that lead to a nervous center in the lumbar portion of the spinal cord. Diabetes mellitus and pernicious anemia also were offered as causes of impotence. Pituitary insufficiency that follows pituitary tumors also was offered as a cause of impotence, and finally

62. Pool, T. L.; Cook, E. N., and Kepler, E. J.: *Endocrine Therapy of Cryptorchidism, Impotence and Prostatic Obstruction*, M. Clin. North America 24:1057-1067 (July) 1940.

the other causes of impotence, such as castration and genital hypoplasia, were discussed.

Pool, Cook and Kepler observed that the vast majority of patients who seek advice because of impotence do not have any demonstrable abnormality of either the genital or the endocrine organs. Skilful questioning almost inevitably reveals the fact that this disability usually is essentially psychogenic. They concluded that endocrine therapy of psychic impotence is virtually worthless.

Concerning the management of benign prostatic obstruction, they concluded that perhaps in the future men suffering from obstruction at the vesical neck may be relieved by some form of endocrine therapy. At present the great majority of such patients will have to submit to operation.

PERIRENAL INSUFFLATION

Ajamil, Romeu, Vega and Montejo⁶³ presented their experience with perirenal insufflation performed 23 times in 19 cases. The procedure was done on the right side in 16 cases and on the left in 7. Three accidents occurred, all on the right side; there were no deaths.

They considered the procedure an exploratory operation that can be suitably practiced in numerous cases, but they stated that it has its dangers, at least with the technic employed at present. This technic must be studied to diminish accidents, and experienced surgeons should practice the exploration. The authors expressed the belief that the method should be used in all doubtful cases, especially in all those in which the presence of renal or pararenal tumors is suspected, when clinical, roentgen or urographic methods do not give an exact diagnosis.

They expressed the opinion that perirenal insufflation must not be used in cases of pyonephrosis or suppurative lesions of the kidney or in those cases in which the urologic procedures actually used, such as roentgen and pyelographic examination, give a complete diagnosis.

They did not recommend for this exploration the use of more than 400 cc. of air or oxygen.

Burhans reported on perirenal insufflation of air as an aid in urologic diagnosis, recording 10 cases to illustrate his data and to show the potential value of the method.

After the usual sterilization of the skin in the lumbar region of an area extending from the costovertebral angle to the crest of the ilium, 1 per cent solution of procaine hydrochloride is infiltrated over the lumbar triangle. The insertion of a no. 24 spinal needle into the perirenal space, with the tip of the needle held well posterior in order to avoid peritoneum and bowel, is the next step. Resistance to the needle

63. Ajamil, L. F.; Romeu, J. G.; Vega, J. M., and Montejo, J. L.: The Role of Perirenal Insufflation in Urology, *J. Urol.* **44**:607-617 (Nov.) 1940.

can be felt as it passes through the perirenal or Gerota's fascia. The next step is to remove the stilet and aspirate with a 10 cc. syringe. If a perirenal abscess is present and accessible, pus will be obtained. If the needle strikes the kidney proper or a blood vessel, blood will be obtained. Under the latter circumstances the needle should be withdrawn and reinserted more posteriorly. Air is then injected into the perirenal area until the patient complains of lumbar fulness and pressure along the fascial layers which extend down into the groin. Usually 30 to 50 cc. of air is used, but at times up to 500 cc. may be injected.

Roentgen exposures have been made in a variety of ways, but the following procedure has been adopted of late: (1) plain urogram; (2) optional, but preferable, intravenous or retrograde pyelograms, prior to the insufflation study; (3) aspiration and insufflation of air, and (4) roentgenograms taken in the anteroposterior and semilateral positions, with direct lateral exposures for visualization of the postrenal space.

Burhans⁶⁴ had not experienced any disabling difficulties from this procedure, such as air embolism, possibly because of the fact that he had been extremely careful in inserting the needle and aspirating to be sure that a blood vessel or the kidney itself had not been punctured; also, owing to the fact that he never injected air into the cavity unless the piston of the syringe slid easily without pressure. He expressed the belief that in order to produce an air embolism air must be injected directly into a vessel or must be present in an area under pressure so that it passes into a vessel.

Moore⁶⁵ stated that perirenal insufflation of air combined with roentgen studies is a procedure which has not been employed to the extent that it deserves as a diagnostic aid.

He had endeavored to demonstrate the thickness of the renal parenchyma in the presence of hydronephrosis by combining perirenal insufflation with pneumopyelography. It is generally known that the excretory dye tests for renal function are not entirely dependable in cases of hydronephrosis. In certain cases in which such tests have indicated an absence of function, subsequent exploration may reveal sufficient remaining renal parenchyma to justify a conservative procedure rather than nephrectomy. In such a case it may be seen that the thickness of the renal cortex in the region of the upper pole is approximately 1 mm.; it is less than 1 cm. in its thickest portion, near the lower pole. In Moore's experience in cases of this type there was no demonstrable function by the usual dye tests, and convincing additional evidence was conveyed by the roentgenograms that a conservative plastic operation

64. Burhans, R. A.: Perirenal Air Insufflation: An Aid in Urological Diagnosis, *J. Urol.* **44**:618-634 (Nov.) 1940.

65. Moore, T. D., in discussion on Burhans,⁶⁴ pp. 635-636.

was hardly worth while, although the opposite hydronephrotic kidney previously had been restored practically to normal by such a conservative operation.

In the employment of insufflation of air a blunt-tipped needle is desirable, as it is less likely to pierce a vessel. The air injected might be compared to subcutaneous emphysema. The last-mentioned condition, even when extensive, is not considered a particularly dangerous complication. It might be mentioned, however, that the employment of insufflation of air as an office procedure is not recommended because of the occasional painful reaction.

Hand⁶⁶ expressed the belief that in problems of precocity, pseudohermaphroditism, hirsutism and masculinism, when studies of the ovaries and pituitary have been completed, the risk involved in arriving at a diagnosis of an adrenal tumor by perirenal injection of air is one that may well be assumed. The risk, however, should not be underestimated, as one will readily realize from a review of the recent literature. Hand had made perirenal air injections for the study of the adrenal gland in 7 cases. In 1 an adrenal tumor was clearly outlined. In the 6 cases in which the results were negative, the films will be of value for comparative purposes as further studies are made.

In the problem of carcinoma of the kidney there are two circumstances that would deter Hand from the use of perirenal injection of air. The first circumstance is the increased risk involved in making a perirenal injection of air in the presence of the large dilated veins that so often accompany the development of collateral circulation in these tumors. The second is that the data obtained by perirenal injection, which suggest that perirenal infiltration of the tumor has occurred, cannot be used as criteria for the operability of renal carcinoma. Hand said this because of the following facts: In 1930 he made a study of 193 cases in which nephrectomy had been carried out for carcinoma of the kidney at the Mayo Clinic. Of the 193 patients subjected to nephrectomy, 24 had lived for ten years or more. The perirenal tissues were involved in 16 (66 per cent) of these cases. It would indeed have been tragic if the right to exploratory operation had been denied to any of these fortunate persons.

Jeck⁶⁷ stated that for the last two years perirenal insufflation had been employed in the urologic service at Bellevue for conditions other than adrenal tumors and that it had proved to be of considerable value. However, he sounded a note of warning, chiefly because of one experience that almost resulted fatally. The test commonly employed to ascertain whether the needle has entered a blood vessel is not necessarily

66. Hand, J. R., in discussion on Burhans,⁶⁴ pp. 636-637.

67. Jeck, H. S., in discussion on Burhans,⁶⁴ pp. 637-638.

reliable; that is, the practice of aspiration to see if there is blood, immediately after the needle is introduced.

The patient in question was a man of about 50 years who had a very large mass in his right loin. The urograms did not explain the condition to Jeck's complete satisfaction, and he thought that injection of air might help. This procedure was tried in the usual manner, with introduction of the needle, apparently in the proper place, and then aspiration. No blood was obtained, and about 100 cc. of air was injected. The patient rapidly became cyanotic and dyspneic. The needle was withdrawn at once, and supportive measures were given; after about ten minutes of restorative treatment the patient was apparently out of danger.

Not satisfied with that experience, Jeck made another attempt at injection of air about two weeks later. The same thing happened, except that on this second occasion the patient looked as though he were most assuredly going to die at once. He recovered again, and it was decided not to repeat the injection of air in his case.

A few days later a transperitoneal exploratory operation was performed under local anesthesia. A very large retrorenal mass was found, part of which evidently had broken down, because a large pocket was encountered in which there was observed first old blood and then some very fresh blood.

The patient died about four months after the exploration. Necropsy revealed an enormous sarcoma behind the kidney. The kidney was apparently normal except that it had suffered from pressure. And, although Jeck had no definite proof that the needles used in the injection of air had entered directly into the sarcoma, it was evident that such was the case. The direction in which the needles had been introduced, the depth of their penetration and the fact that the sarcomatous mass was jammed tightly against the loin made it evident that on both occasions the needles had entered the growth itself.

Fish's⁶⁸ experience with air insufflation dated back to 1926, at which time he began to use this method. Since that time he had employed it in more than 400 cases. No accidents occurred from 1926 to 1937. During the latter year death occurred in 2 of his cases, in each of which the disease was an inoperable malignant tumor. So far as could be determined at necropsy, hemorrhage had not taken place about the site of injection of air. Subsequently Fish employed oxygen, because he believed that it is absorbed more readily and that perhaps nitrogen in the air is the fatal element in producing the embolus.

68. Fish, G. W., in discussion on Burhans,⁶⁴ p. 638.

URINARY ANTISEPTICS

Emmett and Hammer⁶⁹ made a study of the prophylactic use of sulfanilamide to control postoperative infection of the urinary tract. The study was carried out over a period of approximately nine months. The routine procedure adopted was as follows: On the day of the operation 200 cc. of an 0.8 per cent solution of sulfanilamide (25 grains; 1.6 Gm.) was given subcutaneously. This was repeated daily until the patient could tolerate tablets by mouth, at which time the subcutaneous administration of the drug was stopped and the patient was given 15 grains (1 Gm.) daily by mouth in divided doses of 5 grains (0.3 Gm.). In most cases oral administration could be begun on the third postoperative day. If catheterization had not become necessary by the end of the fourth postoperative day, the doses of sulfanilamide were discontinued. If catheterization had been necessary by this time or if a retention catheter was in place, administration of sulfanilamide was continued until the patient left the hospital.

A total of 514 surgical cases were studied. In 262 of these catheterization was required postoperatively. The efficacy of treatment was based solely on the amount of pus found by microscopic examination of the wet smear of a centrifuged catheterized specimen of urine obtained after the patient was dismissed from the hospital.

The incidence of postoperative urinary infection in patients receiving the complete prescribed prophylactic treatment with sulfanilamide was only 25 per cent, while in the group which received no such treatment it was 72.5 per cent. The incidence of postoperative infection of the urinary tract among the patients who received incomplete treatment was 37 per cent.

Struck with the frequency of stitch hole infections and minor breakdowns, particularly in plastic operations on the penis, Young, Hill and Semans⁷⁰ decided to try to prevent these occurrences by administering sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) before operation and continuing to administer the drug afterward for various periods. Although some of the patients were very young children, no serious reactions were encountered. It generally was possible to give the drug without interruption as long as it seemed desirable. The results obtained in 12 cases demonstrated conclusively that by the use of sulfathiazole it is possible to obtain much better healing than heretofore in a large proportion of cases. In addition, it was shown that even when there

69. Emmett, J. L., and Hammer, H. J.: Prophylactic Use of Sulfanilamide to Control Postoperative Infection of the Urinary Tract, *Proc. Staff Meet., Mayo Clin.* **15**:801-806 (Dec. 18) 1940.

70. Young, H. H.; Hill, J. H., and Semans, J. H.: Use of Sulfathiazole Before and After Urologic Operations to Prevent or Combat Infection, *J. Urol.* **44**:714-725 (Nov.) 1940.

had been a small breakdown, under continued therapy with sulfathiazole healing had sometimes taken place, even without the formation of a fistula. In some cases they placed a silver clip to approximate the edges of the breakdown in the skin. Never in their previous experience had this been possible.

Helmholz⁷¹ stated that sulfathiazole is bactericidal for six of the commonest bacteria found in urinary infections. A concentration of 200 mg. per hundred cubic centimeters should prove sufficient for the cure of practically all infections except those due to *Pseudomonas*, which will probably require 300 mg. per hundred cubic centimeters. The effectiveness of the drug for the various bacteria on an ascending scale is as follows: *Pseudomonas aeruginosa*, *Streptococcus faecalis*, *Escherichia coli*, *Aerobacter aerogenes*, *Proteus ammoniae* and *Staphylococcus aureus*. The bactericidal range is from 300 to 25 mg. per hundred cubic centimeters. There is some variation in the effect of the drug at various pH levels, particularly marked with *Str. faecalis*.

URINARY INFECTION

Cook⁷² considered the treatment of resistant infection in the urinary tract. He pointed out that physicians no longer are attempting to eradicate an existing infection without satisfactory knowledge of the type of infection present and without understanding the contributing pathologic processes in the urinary tract and elsewhere. He concluded from this fact that complete urologic examination is necessary in all cases in which the patients do not respond to simple therapy.

Cook advised caution in the use of mandelic acid in cases of impaired renal function and suggested sulfanilamide in some of these cases. The drug to be given subcutaneously if it is not tolerated by mouth. Azo-sulfamide should be used if the latter is not tolerated. Chronic infections in the urinary tract may be cleared up only after foci of chronic infection elsewhere in the body are likewise cleared of infection. It was pointed out that in the treatment of hydronephrosis when marked infection is present it is necessary in some cases to perform a plastic operation to insure adequate drainage before the infection can be eradicated.

The treatment of pyelonephritis associated with calculi is difficult, and here again it may be necessary to resort to surgical operation and removal of the calculi before the infection can be cleared up. In some of these cases of marked infection the use of a nephrostomy tube may be required. Nephrostomy tubes later may be irrigated with various

71. Helmholz, H. F.: The Use of Sulfathiazole as a Urinary Antiseptic. *J. Urol.* 45:135-145 (Jan.) 1941.

72. Cook, E. N.: The Treatment of Resistant Infection in the Urinary Tract. *J. Urol.* 44:191-199 (Aug.) 1940.

solutions, such as acetic acid (1:3,000) or 0.25 to 1 per cent phosphoric acid. The use of 1 ounce (29.5 cc.) of an elixir of aminoacetic acid (56 grains to the ounce [3.6 Gm.]) and 4 Gm. (60 grains) of sodium benzoate daily by mouth is helpful at times in decreasing the tendency to form calculi. Patients who have atrophic pyelonephritis usually require nephrectomy to clear up the infection, assuming that they are having symptoms.

Cook stressed the importance of continued treatment of patients who have cystitis, as the cystitis may recur if the treatment is not given over a long enough period. In addition to chemotherapy, local treatment to the bladder (1) by lavage with solution of boric acid, 1:8,000 solution of potassium permanganate, 0.8 per cent solution of sulfanilamide in physiologic solution of sodium chloride or 1:3,000 solution of acetic acid or (2) by instillation of 7 per cent silver iodide or a solution of 5 per cent mild protein silver may give marked symptomatic relief. In the treatment of cystitis with incrustations the procedure of choice is use of the cystoscope with the patient under anesthesia and topical application of a 20 to 40 per cent solution of silver nitrate. After this a two way indwelling catheter is inserted into the bladder and a solution of silver nitrate starting with a strength of 1:10,000 is used for continuous irrigation for forty-eight to ninety-six hours, the strength being gradually increased to 1:1,000. Finally, it may be necessary to do a suprapubic cystostomy, leaving the tube in place for eight to nine months in order to allow the infection to subside and thus make the patient more comfortable. There are patients who, according to Cook, are frequently overlooked, who have obstruction of the vesical neck. These patients should be treated by transurethral sphincterotomy or resection of the vesical neck.

For chronic infections of the prostate gland Cook recommended a regular course of massage carried out two or three times weekly for eight to twelve weeks. Foci of infection should be excluded, and, finally, it may be necessary to open some chronic ductal abscesses in the prostate gland, whether or not calculi are present in the prostate.

Chronic urethritis in the female is also a difficult lesion to treat. It is best treated by daily application of a urethral tampon saturated with a solution of 2 to 5 per cent strong silver protein for six to ten days. This treatment should be accompanied with occasional dilatation of the urethra with a no. 32 F. sound. It may be necessary to repeat these procedures in six to eight weeks. The application of a soothing ointment to the urethral meatus is also helpful.

Cook divided the more common infections of the urinary tract, excluding tuberculosis, into two main groups: (1) those produced by

a bacillus and (2) those produced by a coccus. There is, however, a third group in which no bacteria can be found even after repeated tests. He also pointed out that there is a tremendous variance in the virulence of different strains of the same organism, as well as in the virulence of different organisms. Furthermore, there is a great variation in the resistance of patients to disease, and these two factors are important in the treatment and management of chronic infections in the urinary tract.

Yeaw⁷³ investigated the lower limit of pH at which growth can occur in urine in vitro for several bacterial species isolated from infections of the urinary tract. A pH level at which death always occurred and a "critical level" at which stasis occurred were estimated for each organism. The conclusions were as follows:

Normal urine is a good culture medium at upper normal pH levels. The urinary pH is relatively stable if the urine is sterile.

The pH level at which death occurs in vitro is at or below the lowest pH levels obtainable by medication for all organisms tested except *Streptococcus haemolyticus* and *Streptococcus viridans*. However, stasis occurs at or above this level for all the organisms except *E. coli* and *A. aerogenes*. It is thus theoretically possible to make the urine bacteriostatic, by acidification alone, for all the organisms tested except *E. coli* and *A. aerogenes*. Bactericidal levels can be reached in this way only for the streptococci. Nevertheless, since infection should be controlled by inhibition of bacterial growth, the pH levels for stasis may be clinically as significant as those necessary to produce death.

In practice, acidification as the sole therapeutic agent has been found useful in some cases. Theoretically its most important use would seem to be prophylactic rather than therapeutic. Indications for its prophylactic application were discussed.

TUBERCULOUS BACILLURIA

Negley and Bogen⁷⁴ stated that pitfalls leading both to false positive and to erroneous negative reports must be avoided in examining for tuberculous bacilluria. Voided specimens and other urine in contact with sources of contamination, inadequate decolorization or incorrect identification may yield false positive data, while insufficient specimens, incomplete staining or excessive decolorization or counterstaining, hasty examination and the omission of concentration, culture and animal inoculation technics may result in the overlooking of organisms actually present.

73. Yeaw, R. C.: The Effect of pH on the Growth of Bacteria in Urine, *J. Urol.* 44:699-712 (Nov.) 1940.

74. Negley, J. C., and Bogen, E.: The Tuberculin Skin Test in Guinea Pigs Injected with Suspected Urine Sediment, *J. Urol.* 44:860-863 (Dec.) 1940.

The inoculation of urinary sediment into guinea pigs is a more sensitive and reliable test than are microscopic or cultural methods for the detection of tubercle bacilli, but is much slower. The use of the tuberculin cutaneous test in these animals greatly shortens the time required. A cutaneous test with 5 mg. of old tuberculin injected intracutaneously in a guinea pig reveals the presence or absence of tuberculous infection in 99 per cent of the animals tested within a month of the date of inoculation.

ANESTHESIA

Engel, Cushnie, Livingstone and Shank⁷⁵ presented their results with various anesthetics in a series of 2,059 consecutive operations on the genitourinary tract.

Morphine sulfate, 0.010 or 0.015 Gm., given one hour before operation, was generally used for adults before inhalation anesthesia. Resistant patients also received pentobarbital sodium or sodium phenobarbital, the doses being chosen individually. Children received codeine sulfate or one of the barbiturates, alone or in combination. For spinal anesthesia, 0.010 Gm. of morphine sulfate hardly ever was exceeded.

Procaine crystals were used exclusively for spinal anesthesia operations on the genitourinary tract. The amount varied depending on the desired level of anesthesia and the presumable duration of the operation. For cystoscopies and endovesical operations the average amount was 75 to 120 mg. of procaine hydrochloride dissolved in 2.5 to 3 cc. of spinal fluid. For suprapubic procedures 120 to 150 mg. procaine hydrochloride in 4 cc. of spinal fluid was employed. The lumbar puncture was usually performed between the third and the fourth lumbar vertebra. Except for patients with hypertension, ephedrine sulfate, 0.048 Gm., was administered hypodermically before the spinal anesthetic was given. Hypertensive patients received half the dose of ephedrine or none, depending on the degree of hypertension. Patients with hypotension were given double the aforementioned amount of ephedrine, and the spinal anesthetic was not administered unless a satisfactory response was obtained. In the 764 instances in which a spinal anesthetic was administered in this series of cases, 91 patients received no ephedrine before anesthesia.

Engel, Cushnie, Livingstone and Shank expressed the opinion that an ethylene-oxygen mixture is the anesthetic of choice for renal operations. It is free from toxic effects on the kidneys, heart and circulation if anoxia is prevented. It is potent enough to allow a sufficient per-

75. Engel, R.; Cushnie, E.; Livingstone, H., and Shank, I.: Anesthetic Results in Urogenital Surgery: A Report of 2,059 Operations. *J. Urol.* 45:124-134 (Jan.) 1941.

centage of oxygen. The patient who has diabetes or pulmonary disease is not harmed by it. Since cautery is not employed in this type of surgical procedure, the danger of explosion does not contraindicate the use of ethylene and oxygen, provided due precaution is taken to prevent static sparks.

Ethylene-oxygen anesthesia alone was used in more than four fifths of all cases in which renal operations were performed, that is, 359 times. A small quantity of ether had to be added in 64 instances to obtain surgical anesthesia. In only 12 cases were spinal anesthetics given for renal surgical operations. These were cases in which it was assumed that surgical anesthesia could not be established without the addition of large amounts of ether and cases in which the use of ether was contraindicated. The high level of anesthesia required frequently causes a fall in blood pressure and depresses respiration.

Suprapubic cystotomy, if used as the first stage of suprapubic prostatectomy, usually is performed with local infiltration anesthesia. In the majority of cases the patients are aged and in poor general condition. Spinal anesthesia was chosen for cystotomy with endovesical surgical operation in which the electric cautery was employed and when good relaxation was essential. In this series suprapubic prostatectomy was performed more frequently with ethylene-oxygen anesthesia. Encouraged by favorable results in other fields with spinal anesthesia, the authors recently had employed this method with satisfactory results in an increasing number of suprapubic prostatectomies.

Nitrogen monoxide and oxygen anesthesia was employed for simple cystoscopy when relaxation was not required. Cystoscopy with endovesical surgical procedure, as well as most of the intraurethral procedures, was performed with spinal anesthesia. If inhalation anesthesia was necessary, nitrogen monoxide and oxygen was used because of the hazard of explosion from the electrical devices employed. Practically all of the transurethral electroresections of the prostate were performed under spinal anesthesia. Several years ago, transsacral-caudal blocks were employed but were abandoned in favor of spinal anesthesia because the surgeon believed the position necessary for their induction to be inadvisable for elderly patients who were poor risks. This method also was somewhat more time consuming and painful than spinal anesthesia.

A study of the risks, the anesthetic agents and the complications which occurred during operation in the respective groups, revealed interesting facts. The administration of stimulating drugs, which was made necessary by the patient's condition, is the index of the incidence of fall in blood pressure, or so-called shock, in the group in which spinal anesthesia was used.

There was a low incidence of postoperative pneumonia after spinal anesthesia. Hemorrhage and shock occurred in about the same per-

centage in both anesthetic groups. The high incidence of uremia after general anesthesia seemed to be due to the fact that the type of operation most frequently complicated by uremia was performed under general anesthesia. It is interesting to note that in no case did coronary occlusion follow spinal anesthesia, in spite of the fact that a large number of patients had cardiovascular disease.

The total mortality rate was 2.3 per cent. The greatest number of deaths (5 per cent) occurred after operations performed under local anesthesia. Local anesthesia had been employed because of the serious condition of the patients, as comparison with the preoperative risks suggests.

The higher incidence of deaths from heart failure after inhalation anesthesia than after spinal anesthesia is interesting. Anoxemia produced when the patient was under nitrogen monoxide and oxygen anesthesia was the contributing factor in 1 death. More deaths occurred from pneumonia after spinal anesthesia than after inhalation anesthesia. In the majority of instances, however, the pneumonia was terminal.

ANESTHETIC EFFECT OF PYRIDIUM

Morrissey and Spinelli⁷⁶ studied a series of 103 cases of common urogenital infections to determine the analgesic effects of pyridium (phenylazo- α - α -diaminopyridine monohydrochloride). The relief of the distressing subjective symptoms of common urogenital infections, such as dysuria, pollakiuria, incontinence, backache at a low level, pain in the costovertebral triangle, pain in the region of the ureter, suprapubic pain, and various referred pains, was evaluated.

A series of 19 urologic surgical cases was studied for the effects of pyridium on preoperative and postoperative subjective symptoms. In these cases wound anesthesia and general analgesia were produced to such a degree that the need for narcotics was minimal.

A series of 130 cases was studied to determine the local analgesic effects of pyridium during diagnostic instrumentation. The results were stated to be adequate and satisfactory.

SACRAL ANESTHESIA

Tuohy and Adams⁷⁷ described sacral block anesthesia with special reference to urologic practice. They found that this anesthesia is indicated for transurethral operations and cystoscopic procedures, especially for patients who are debilitated and who are not considered

76. Morrissey, J. H., and Spinelli, A. N.: An Experimental Study of the Anesthetic and Analgesic Properties of Pyridium, *J. Urol.* **44**:381-385 (Sept.) 1940.

77. Tuohy, E. B., and Adams, R. C.: Sacral Block Anesthesia, with Special Reference to Urologic Practice, *Anesth. & Analg.* **19**:291-292 (Sept.-Oct.) 1940.

good surgical risks. The advantages are: (1) less fluctuation in systolic blood pressure; (2) less danger of development of surgical shock, and (3) less nausea and vomiting. The disadvantages are: (1) delayed or incomplete anesthesia and (2) priapism in male patients. They recommended the use of metycaine for injection and claimed that it is no more toxic than procaine.

GENITOURINARY ALLERGY

Johnson⁷⁸ stated that there are urologic symptoms which appear to be correlated with other conditions having an allergic basis and that treatment of the allergy should be undertaken by the urologist when such conditions directly affect the relief of recurrent genitourinary symptoms.

Allergy is not a specific protein sensitization but a constitutional state of hypersensitivity or lowered resistance, produced by an avitaminosis associated with disturbed mineral metabolism.

Local or general symptoms of allergy are provoked by increased absorption, retention or failure of the body properly to detoxify the toxic amino acids, chief among which is histamine.

Relief of the allergic state is not dependent on specific protein desensitization but more logically should be brought about through replacement of deficiencies ascertained in the individual case, not only by balancing the diet but by mineral and vitamin therapy.

Histaminase is the natural enzyme neutralizing histamine and is derived from the intestinal mucosa and the liver, which are the natural detoxifying agents of the body, acting as a protective phenomenon against the absorption of the toxic products of putrefaction from the intestinal tract. Histamine desensitization therapy for the relief of allergic symptoms is more logical than the older method of desensitizing against specific proteins, principally because it does not interfere with the normal balanced diet so essential in these cases, nor does it interfere with the economic and geographic environment of the patient.

ARTIFICIAL DIURESIS

Helmholz and Bollman,⁷⁹ in an experimental study, attempted to find what solution producing minimal harm to the tissues produces the maximal diuresis. Rabbits were the experimental animals, and solutions of sucrose, dextrose, sorbitol, urea and sodium sulfate were used.

78. Johnson, H. McC.: Histaminase and Histamin Desensitization in Genito-Urinary Allergy, *J. Urol.* 43:891-905 (June) 1940.

79. Helmholz, H. F., and Bollman, J. L.: The Intravenous Administration of Sucrose Solutions as a Means of Producing Intense Diuresis, *J. Lab. & Clin. Med.* 25:1180-1187 (Aug.) 1940.

Diuresis was obtained by intravenous injection of 20 per cent solutions of sucrose. Marked hydropic degeneration of the convoluted tubules occurred, and in twenty-four to forty-eight hours there was marked lowering of the content of phenolsulfonplthalein and temporary anuria occasionally developed. These changes produced no permanent damage, however, and after thirty-nine days the kidney could not be distinguished grossly or microscopically from a normal kidney. Sodium sulfate, urea, dextrose and sorbitol equivalent to 20 per cent sucrose produced less diuresis in every case. With the exception of sorbitol, all were definitely more toxic than sucrose. To avoid lethal effects of intense diuresis it was found that 8 per cent sucrose solution in one-half strength Ringer's solution should be used.

Correspondence

AN APOLOGY

To the Editor:—Our attention has been called to the fact that in our paper "Vertebral Compression Fractures Sustained During Convulsions," in the March issue (ARCH. SURG. 42:550, 1941), we used material from an article by Dr. O. Theodore Roberg Jr. which appeared in the July 1937 issue of the *Journal of Bone and Joint Surgery* without giving credit to the author.

We wish to apologize for our action, which would appear to be deliberate plagiarism. The original manuscript, prepared by Dr. Androp in longhand, shows quotation marks before and after the material quoted. Our intention was to give Dr. Roberg full credit, but the quotation marks were inadvertently omitted in the typing of the material from the longhand manuscript.

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STUDIES ON EXPERIMENTAL HYPERTENSION

XV. EXPERIMENTAL OBSERVATIONS ON HYPERTENSION ASSOCIATED WITH UNILATERAL RENAL DISEASE; EFFECT OF OCCLUSION OF THE URETER ON EXPERIMENTAL HYPERTENSION DUE TO UNILATERAL RENAL ISCHEMIA

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LOS ANGELES

In the earliest studies on experimental hypertension due to renal ischemia¹ it was shown that constriction of the main artery of only one kidney in a dog or a monkey is sufficient to cause elevation of the blood pressure. It was also shown in these and in later studies² that this elevation does not usually persist indefinitely unless the other kidney is removed or unless the main artery of the other kidney is also constricted.

From the Institute of Pathology, the Western Reserve University.

A preliminary report was presented before the Central Society for Clinical Research, Chicago, Nov. 1, 1940.

This study was supported by the Beaumont Trust (L. D. Beaumont) and the Josiah Macy Jr. Foundation. It was aided by grants from Mr. Nathan Richman, Mr. Richard Kohn, Mr. Nathan Dauby and Mr. Alex Wintner and his associates, of Cleveland.

1. (a) Goldblatt, H.; Lynch, J.; Hanzal, R. F., and Summerville, W. W.: Studies on Experimental Hypertension: I. The Production of Persistent Elevation of Systolic Blood Pressure by Means of Renal Ischemia, *J. Exper. Med.* **59**: 347 (March) 1934. (b) Goldblatt, H.: Studies on Experimental Hypertension: III. The Production of Persistent Hypertension in Monkeys (Macaque) by Renal Ischemia, *ibid.* **65**:671 (May) 1937.

2. Goldblatt, H.: (a) Studies on Experimental Hypertension: V. The Pathogenesis of Experimental Hypertension Due to Renal Ischemia, *Ann. Int. Med.* **11**:69 (July) 1937; (b) Experimental Hypertension Induced by Renal Ischemia, in Harvey Lectures, 1937-1938, Baltimore, Williams & Wilkins Company, 1938, pp. 237-275; *Bull. New York Acad. Med.* **14**:523 (Sept.) 1938; (c) Studies on Experimental Hypertension: XII. The Experimental Production and Pathogenesis of Hypertension Due to Renal Ischemia, *Am. J. Clin. Path.* **10**:40 (Jan.) 1940.

In most dogs with unilateral renal ischemia the blood pressure returns to the preoperative level in six weeks or less, but in some the hypertension may persist at a high level for many months. The return of the blood pressure to normal obviously may be due (a) to the development of considerable accessory circulation to the ischemic kidney or (b) to the compensating, neutralizing or inhibiting effect of the contralateral normal kidney. The way in which this mechanism acts is not yet known. In this connection, the significant observation was also made that if the single ischemic kidney is removed after a short or even a long period of hypertension the blood pressure usually returns to the preoperative level in twenty-four to forty-eight hours and remains at this level.^{2a} These observations have all been fully confirmed by other investigators.³

The existence in man of hypertension associated with bilateral chronic pyelonephritis has been recognized⁴ for some time. Recently an exhaustive treatise on the subject has been written.⁵ The experimental production of hypertension by constriction of one main renal artery and the cure of the hypertension by removal of the ischemic kidney have led to the recognition of hypertension associated with unilateral chronic pyelonephritis in man as well as to the successful treatment of this condition by the removal of the diseased kidney when the other kidney is normal. In man, as in some dogs, the hypertension evidently may persist for a long time on the basis of unilateral renal disease. There have been reported cases of human hypertension associated not only with unilateral

3. (a) Wood, J. E., and Cash, J. R.: Experimental Hypertension: Observations on Sustained Elevation of Systolic and Diastolic Blood Pressure in Dogs. *J. Clin. Investigation* **15**:543 (Sept.) 1936. (b) Elaut, L.: Observations concernant l'hypertension chronique expérimentale du chien par constriction de l'artère rénale, *Compt. rend. Soc. de biol.* **123**:1244 (Nov.) 1936. (c) Page, I. H., and Sweet, J. E.: Extirpation of Pituitary Gland: Effect on Arterial Blood Pressure of Dogs with Experimental Hypertension, *Proc. Soc. Exper. Biol. & Med.* **34**:260 (March) 1936. (d) Blalock, A., and Levy, S. E.: Studies on the Etiology of Renal Hypertension, *Ann. Surg.* **106**:826 (Nov.) 1937. (e) Verney, E. B., and Vogt, M.: An Experimental Investigation into Hypertension of Renal Origin, with Some Observations on Convulsive "Uraemia," *Quart. J. Exper. Physiol.* **28**:253 (Sept.) 1938. (f) Fasciolo, J. C.; Houssay, B. A., and Taquini, A. C.: The Blood Pressure Raising Secretion of the Ischemic Kidney, *J. Physiol.* **94**:281 (Dec.) 1938. (g) Gibson, J. G., II., and Robinson, R. W.: Blood Volume, Cardiac Size and Renal Function in Dogs with Hypertension Produced by Goldblatt Technique, *Proc. Soc. Exper. Biol. & Med.* **39**:497 (Dec.) 1938. (h) Katz, L. N.; Friedman, M.; Rodbard, S., and Weinstein, W.: Observations on the Genesis of Renal Hypertension, *Am. Heart J.* **17**:334 (March) 1939.

4. Löhlein, M.: Ueber Schrumpfnieren, *Beitr. z. path. Anat. u. z. allg. Path.* **63**:570, 1917. Longcope, W. T.: Chronic Bilateral Pyelonephritis: Its Origin and Its Association with Hypertension, *Ann. Int. Med.* **11**:149 (July) 1937.

5. Weiss, S., and Parker, F., Jr.: Pyelonephritis: Its Relation to Vascular Lesions and to Arterial Hypertension, *Medicine* **18**:221 (Sept.) 1939.

chronic pyelonephritis (with or without calculus) ⁶ but with unilateral vascular disease, including thrombosis and embolism, with or without infarction; kinking, anomaly or aneurysm of the main renal artery ⁷; tumor of one kidney ⁸ and urinary obstruction due to a variety of patho-

6. (a) Butler, A. M.: Chronic Pyelonephritis and Arterial Hypertension, *J. Clin. Investigation* **16**:889 (Nov.) 1937. (b) Barker, N. W., and Walters, W.: Hypertension Associated with Unilateral Chronic Atrophic Pyelonephritis: Treatment by Nephrectomy, *Proc. Staff Meet., Mayo Clin.* **13**:118 (Feb. 23) 1938. (c) Crabtree, E. G.: Hypertension in Destructive Infected Unilateral Lesions of the Kidney, *Tr. Am. A. Genito-Urin. Surgeons* **31**:299 (May) 1938. (d) Barney, J. D., and Suby, H. I.: Unilateral Renal Disease with Arterial Hypertension: Report of a Case Apparently Cured Following Nephrectomy, *New England J. Med.* **220**:744 (May 4) 1939. (e) McIntyre, D. W.: Unilateral Chronic Pyelonephritis with Arterial Hypertension, *J. Urol.* **41**:900 (June) 1939. (f) Nesbit, R. M., and Ratliff, R. K.: Hypertension Associated with Unilateral Nephropathy, *ibid.* **43**:427 (March) 1940. (g) Schroeder, H. A., and Fish, G. W.: Studies on "Essential" Hypertension: III. The Effect of Nephrectomy upon Hypertension Associated with Organic Renal Disease, *Am. J. M. Sc.* **199**:601 (May) 1940. (h) Braasch, W. F.; Walters, W., and Hammer, H. J.: Hypertension and the Surgical Kidney, *J. A. M. A.* **115**:1837 (Nov. 30) 1940. (i) Mulholland, S. W.: Hypertension's Challenge to Urology, *J. Urol.* **42**:957 (Dec.) 1939. (j) Engel, W. J.: Association of Unilateral Kidney Disease with Hypertension, *Cleveland Clin. Quart.* **7**:290 (Oct.) 1940. (k) Salley, S. M.: Hypertension Due to Unilateral Kidney Disease, *Bull. Jackson Mem. Hosp.* **3**:10 (Jan.) 1941. (l) Maher, C. C., and Wosika, P. H.: Urologic Hypertension: A Study of 101 Cases, *J. Urol.* **41**:893 (June) 1939. (m) Bothe, A. E.: Pyelonephritis in Children and Adults with Hypertension, *ibid.* **42**:969 (Dec.) 1939. (n) Patch, F. S.; Rhea, L. J., and Codnere, J. T.: Hypertension in a Girl of Twelve, Associated with Unilateral, Chronic, Atrophic Pyelonephritis Treated by Nephrectomy, *Canad. M. A. J.* **43**:419 (Nov.) 1940. (o) Kennedy, R. L. J.; Barker, N. W., and Walters, W.: Malignant Hypertension in a Child: Cure Following Nephrectomy, *Am. J. Dis. Child.* **61**:128 (Jan.) 1941.

7. (a) Moritz, A. R., and Oldt, M. R.: Arteriolar Sclerosis in Hypertensive and Non-Hypertensive Individuals, *Am. J. Path.* **13**:679 (Sept.) 1937. (b) Leadbetter, W. F., and Burkland, C. F.: Hypertension in Unilateral Renal Disease, *J. Urol.* **39**:611 (May) 1938. (c) Boyd, C. H., and Lewis, L. G.: Nephrectomy for Arterial Hypertension, *ibid.* **39**:627 (May) 1938. (d) Blackman, S. S., Jr.: Arteriosclerosis and Partial Obstruction of the Main Renal Arteries in Association with "Essential" Hypertension in Man, *Bull. Johns Hopkins Hosp.* **65**:353 (June) 1939. (e) Howard, T. L.; Forbes, R. P., and Lipsecomb, W. R.: Aneurysm of the Left Renal Artery in a Child Five Years Old with Persistent Hypertension, *J. Urol.* **44**:808 (Dec.) 1940. (f) Saphir, O., and Ballinger, J.: Hypertension (Goldblatt) and Unilateral Malignant Nephrosclerosis, *Arch. Int. Med.* **66**:541 (Sept.) 1940.

8. Pincoffs, M. C., and Bradley, J. E.: The Association of Adenosarcoma of the Kidney (Wilms' Tumor) with Arterial Hypertension, *Tr. A. Am. Physicians* **52**:320, 1937. Koons, K. M., and Ruel, M. K.: Hypertension in a Seven Year Old Girl with Wilms' Tumor Relieved by Nephrectomy, *J. A. M. A.* **115**:1097 (Sept. 28) 1940.

logic conditions,^{8a} all of which can be considered examples of unilateral renal ischemia.^{8a} The return of the blood pressure to normal as a result of removal of an ischemic kidney has already been reported⁹ in cases of hypertension in man in which one kidney was diseased and the other was evidently normal or not significantly diseased. In personal communications to us there have been mentioned at least 25 additional cases in which unilateral nephrectomy has resulted in the return of the blood pressure to normal for periods varying from three months to two and one-half years. In most of these cases the disease was unilateral chronic pyelonephritis, with the usual intrarenal vascular changes that accompany this condition.

In man, when the presence of disease in one kidney is established it is often difficult to determine with certainty whether the other kidney is diseased and especially whether it is the seat of arteriosclerosis or arteriolar sclerosis. All studies of the other, presumably normal kidney, including clearance tests of various kinds for renal excretory function, may give results within the limits of normal; nevertheless, the kidney may be the seat of considerable vascular disease. It is impossible, therefore, to predict with certainty the probable effect on hypertension in man of removal of one obviously diseased kidney. If the other kidney is normal, the probability is great, in the light of the experimental studies on animals and the results already obtained from unilateral nephrectomy in man, that the blood pressure will return to normal after removal of the diseased kidney. If the other kidney is known to be diseased or if its excretory function is found to be somewhat impaired, unilateral nephrectomy is not indicated as a treatment for the hypertension alone and should be practiced only if it is considered advisable for the renal disease itself. This conclusion is in agreement with the views of others who have recently reviewed this subject.¹⁰ Excision of the more diseased of two diseased kidneys for the sole purpose of possibly alleviating the hypertension is certainly not justifiable.^{6g}

The results of the following experiments are of interest in connection with the general problem of the pathogenesis of hypertension due to renal ischemia and may also prove of value in solving the clinical problem whether or not to perform unilateral nephrectomy for the purpose of lowering the blood pressure in some cases of hypertension in man in which one kidney is obviously diseased and probably ischemic.

8a. Since this paper was submitted for publication, an exhaustive review, with complete bibliography, on the subject of human hypertension associated with unilateral renal disease has been published by B. S. Abeshouse (*Surgery* 9:942 [June] 1941; 10:147 [July] 1941).

9. Footnote 6. Footnote 7 b, c and d.

10. Footnote 6 g, h, i and l.

EXPERIMENTS

Effect on the Blood Pressure of Dogs of Unilateral Constriction of the Main Renal Artery.—On the basis of considerable experience, it has become justifiable to expect significant elevation of the blood pressure in most dogs as a result of

TABLE 1.—*Effect of Constriction of One Main Renal Artery on the Blood Pressure of the Dog*

Dog	Preoperative Period					Postoperative Period				
	Average Weekly Blood Pressure, Mm. Hg				Maximum on Any Day	Average Weekly Blood Pressure, Mm. Hg				Maximum on Any Day
	1st	2d	3d	4th		1st	2d	3d	4th	
247.....	120	125	120	120	140	120	135	150	152	160
248.....	130	125	130	120	130	127	150	138	148	155
250.....	147	135	141	145	150	156	180	182	175	185
253.....	150	145	145	140	160	171	190	175	150	190
267.....	143	134	137	135	150	161	190	208	201	215
268.....	163	166	162	160	175	180	223	228	245	250
305.....	155	150	145	150	160	171	188	190	200	215
306.....	135	135	140	130	155	165	164	150	162	195
307.....	145	150	147	136	170	154	164	182	180	200
313.....	142	148	154	152	160	183	183	175	170	210
319.....	135	135	130	133	140	148	160	165	160	165
326.....	155	155	140	152	160	161	177	165	165	190
333.....	135	120	120	130	140	155	172	175	170	180
335.....	130	135	132	132	145	164	172	175	158	185
336.....	120	125	137	123	135	134	130	138	135	150
339.....	130	125	123	125	130	147	160	160	160	165
340.....	150	140	145	130	150	140	152	147	145	160
342.....	140	135	135	137	140	178	170	172	173	200
377.....	145	145	150	140	150	156	168	148	148	170
384.....	150	125	125	133	160	158	168	165	160	175
417.....	145	140	145	140	145	151	170	165	160	170
428.....	145	140	145	140	160	148	154	155	150	165
433.....	110	110	108	114	120	143	150	143	160	160
434.....	130	125	135	130	145	148	174	186	195	200
461.....	130	130	135	130	135	140	155	155	148	170
503.....	145	130	140	130	160	174	168	155	170	185
507.....	160	160	150	145	160	168	198	183	180	215
532.....	125	120	125	122	145	154	160	150	148	165
538.....	145	143	145	135	155	152	163	173	168	180
539.....	120	125	120	135	140	144	147	133	130	155
549.....	145	143	143	138	150	155	164	162	160	170
590.....	125	125	130	128	135	137	138	130	120	145
640.....	115	120	120	110	120	129	152	150	143	170
646.....	115	110	112	118	120	137	148	145	140	155
679.....	135	137	130	125	140	136	157	152	145	160
680.....	118	112	110	103	130	129	128	122	125	145
686.....	140	125	130	127	140	120	129	120	120	135
701.....	115	115	115	110	115	127	135	133	133	155
702.....	125	115	110	115	125	136	150	150	127	140
729.....	110	105	115	112	120	138	127	121	132	145
Aver. values.	136	132	133	131	144	150	161	159	158	175

adequate constriction of the main artery of only one kidney. Inadequate or excessive constriction of only one main renal artery may fail to cause significant elevation of blood pressure or may cause slight elevation which persists for only a few days. Adequate constriction almost invariably results in a significant but variable elevation of the blood pressure. Table 1 gives the average weekly values for the direct femoral blood pressure of 40 dogs during a preoperative period of four weeks and during an equal period after constriction of one main renal artery. The maximum pressures for the two periods are also given. In these dogs, after the control period the main artery of one kidney was constricted to a variable degree by means

of a silver clamp by the method previously described.¹¹ All operations were performed with the dogs under ether anesthesia after the previous injection of morphine and atropine. The direct mean blood pressure was determined by the insertion (through skin and fascia) into the femoral artery of a 21 gage needle connected by a liquid system (2 per cent sodium citrate) with a mercury manometer. The data in table 1 show that in 40 dogs, almost without exception, there was a statistically significant elevation of the average direct femoral blood pressure during all of the first four weeks after constriction of the main artery of only one kidney. In some of the dogs the elevation was great; in others it was only slight. It is evident from this chart, even without special statistical analysis, that in the dog, at least, a significant but variable rise of blood pressure almost invariably results from adequate constriction of only one main renal artery.

Effect on the Blood Pressure of the Dog of Occlusion of the Ureter of One Kidney.—In 6 dogs the ureter of one kidney was occluded. The surgical incision and retroperitoneal approach were the same as for the application of a clamp on the main renal artery for the production of renal ischemia.¹¹ The ureter was isolated for a short distance, tied by means of four ligatures and cut so that two ligatures were left on each end. To insure permanent occlusion of both ends, the two ligatures on each cut end were then tied together.

There was no significant elevation of blood pressure at any time in any of the animals as a result of this procedure.

Effect on the Blood Pressure of the Dog of Unilateral Constriction of the Main Artery and Occlusion of the Ureter of the Same Kidney.—The purpose of this study was to determine whether unilateral renal ischemia of the degree that practically always results in elevation of blood pressure (table 1) would be effective if at the same time the excretory function of the ischemic kidney were completely arrested by occlusion of the ureter, which alone does not result in elevation of the blood pressure.

In 20 dogs, after a control period of four weeks a clamp was applied to the main artery of one kidney and the vessel constricted to a degree that is practically always (table 1) followed by some elevation of blood pressure. At the same time the ureter of this kidney was ligated and transected in the manner previously described. Table 2 shows that in 19 of these animals there was no significant elevation of blood pressure after the operation. In these animals, neither the average pressure for all of the four weeks after the operation nor the maximum pressure during any day of this period showed a significant change from the preoperative control values. Only 1 animal, dog 5-74 (table 2), showed any elevation of blood pressure during the postoperative period, and in this dog a ureteral fistula developed which lasted for about three weeks after the operation. When the fistula closed (spontaneously), the blood pressure promptly fell to normal. The first part of chart 2 (dog 5-86) is a typical illustration of the effect of constriction of the main artery and occlusion of the ureter of one and the same kidney.

Comment.—These results are in striking contrast to the effect on the blood pressure of unilateral renal ischemia due to constriction of one main renal artery alone, without interference with the ureter (table 1), and they show that in the dog ischemia in a kidney which is nonfunctioning

11. Goldblatt (footnotes 1 and 2 c).

so far as excretion of urine is concerned does not produce elevation of blood pressure. The failure of the blood pressure to rise, especially during the first two weeks after constriction of one main renal artery and coincident occlusion of the ureter, at a time when there is still a considerable amount of renal parenchyma, is the significant result. The absence of any effect on the blood pressure later, at a time when the renal parenchyma is in great part destroyed by hydronephrosis, is not surprising. Whether it means that the chemical substance of renal origin¹² which probably determines hypertension due to renal ischemia is not or cannot be formed in such a kidney, that it is formed in a quantity inade-

TABLE 2.—*Effect of Constriction of One Main Renal Artery and Occlusion of the Ureter of the Same Kidney on the Blood Pressure of the Dog*

Dog	Preoperative Period					Postoperative Period				
	Average Weekly Blood Pressure, Mm. Hg				Maximum on Any Day	Average Weekly Blood Pressure, Mm. Hg				Maximum on Any Day
	1st	2d	3d	4th		1st	2d	3d	4th	
404.....	140	138	138	138	140	127	128	122	127	140
491.....	131	117	121	126	140	127	132	125	120	140
493.....	123	117	115	117	130	126	115	120	122	130
530.....	127	125	135	142	145	135	132	122	122	145
537.....	121	120	103	120	125	125	125	125	110	135
540.....	134	134	133	135	145	144	140	126	135	155
553.....	140	126	120	128	150	123	124	126	125	140
563.....	123	125	123	123	130	123	122	125	123	130
574.....	110	120	115	116	120	140	124	130	120	145
584.....	126	122	125	128	135	128	125	122	120	135
586.....	126	125	138	128	140	131	126	122	123	135
597.....	145	135	145	143	150	131	125	128	123	135
598.....	155	150	155	157	160	154	146	140	140	160
599.....	140	140	134	143	150	137	133	132	133	145
600.....	125	133	128	130	140	125	125	118	119	135
600.....	145	141	132	130	145	134	144	135	135	145
623.....	125	125	120	130	150	127	125	128	115	135
645.....	135	125	120	130	135	133	131	120	115	155
663.....	125	125	125	128	135	125	127	123	120	135
708.....	120	115	120	118	125	119	118	118	112	125
Aver. values.	131	128	128	131	140	131	128	126	123	140

quate to be effective in the presence of one normal kidney or that it is formed in the same quantity as in any ischemic kidney but does not enter the blood stream in a substantial quantity in a given time, on account of the greatly reduced outflow of blood from the kidney, is answered, at least in part, by the following experiments.

Effect on Blood Pressure of Occlusion of the Ureter of the Ischemic Kidney in a Dog with Hypertension Due to Unilateral Constriction of the Main Renal Artery.—In 4 dogs with definitely elevated blood pressure resulting from constriction of the main artery of one kidney the ureter of this kidney was ligated and transected. As a result, there was a fall of the blood pressure to normal. Occlusion of the ureter was carried out at a time when a natural return of the blood pressure

12. Goldblatt.² Fasciolo and others.^{2f}

to normal was not expected, and the drop of the blood pressure to normal, although it took from three to seven days, was more rapid than is usual in an animal with unilateral renal ischemia. The fact that the fall to normal required several days indicates that the substance from the ischemic kidney which brings about the pressor effect continued to enter the circulation in sufficient quantity at least for several days after the ureter was occluded. Chart 1 (dog 7-78) is illustrative of all 4 experiments. The effect of occlusion of the ureter on the blood pressure can be interpreted as due either to gradual interference with the entrance of the pressor-producing substance into the circulation or to a gradual cessation of its formation as the hydronephrosis developed.

Effect on the Blood Pressure of Dogs of Constriction of the Main Arteries and Occlusion of the Ureters of Both Kidneys.—In 3 dogs the main artery of one kidney was moderately constricted and the ureter of the same kidney occluded in the same operation. As soon as it was certain that this had failed to affect the blood pressure, the same procedures were carried out on the other kidney. The invariable result

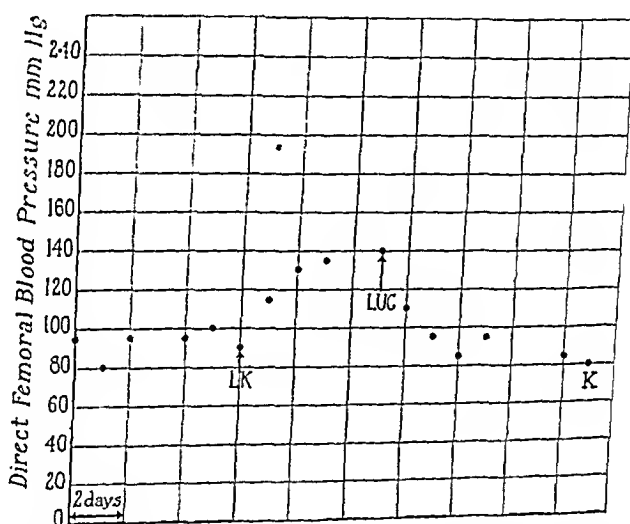


Chart 1 (dog 7-78).—Effect on blood pressure of occlusion of the ureter after the blood pressure has become elevated owing to constriction of the main artery of one kidney. *LK*, moderate constriction of the left main renal artery. *LUC*, occlusion by ligation and transection of the left ureter. *K*, killed.

was uremia, as in the case of excessive constriction or occlusion of both main renal arteries¹³ or occlusion of both ureters, and this was accompanied, as in the conditions just mentioned, by slight to moderate elevation of blood pressure. The animals with uremia and considerable hypertension developed the typical arteriolar lesions of the malignant phase of experimental hypertension due to excessive renal ischemia, previously described.¹⁴ Chart 2 (dog 5-86) is illustrative of the 3 experi-

13. Footnotes 1 and 2.

14. Goldblatt, H.: Studies on Experimental Hypertension: VII. The Production of the Malignant Phase of Hypertension, *J. Exper. Med.* 67:899 (May) 1938; Studies on Experimental Hypertension: XIII. Experimental Observations on the Malignant Phase of Essential Hypertension; the Production of Intrarenal

(Footnote continued on next page)

ments. Thus, in animals with both kidneys ischemic owing to constriction of the main arteries and with the ureters occluded as well the result was not like that of bilateral nephrectomy, which does not produce elevation of blood pressure,^{2b} but more like that of excessive constriction of one main renal artery with occlusion of the ureter of the other kidney.¹⁴ The absence of the inhibitory, neutralizing or compensating effect of a normal kidney¹⁵ evidently resulted in elevation of the blood pressure due to entrance into the circulation of an otherwise inadequate amount of pressor-producing substance.

Effect on the Blood Pressure of the Dog of Constriction of the Main Artery and Occlusion of the Ureter of One Kidney, with Contralateral Nephrectomy.—In 3 dogs the main artery of one kidney was moderately constricted and the ureter tied and cut as has been described. After four to six days, during which time there was no significant rise of blood pressure and before much destruction of renal parenchyma

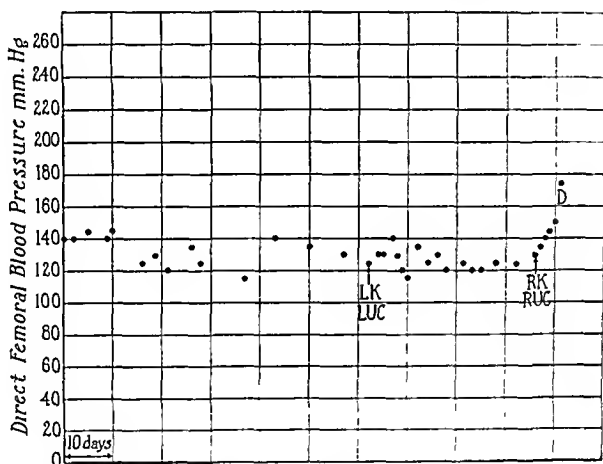


Chart 2 (dog 5-86).—Effect on blood pressure of constriction of both main renal arteries and occlusion of both ureters. *LK*, moderate constriction of the left main artery. *LUC*, occlusion of left ureter. *RK*, constriction of right main renal artery. *RUC*, occlusion of right ureter. *D*, died.

by hydronephrosis could occur, the other kidney was excised. In both animals there was then a moderate but significant elevation of the direct femoral blood pressure, which was evident about twenty-four hours after nephrectomy and persisted until the animal died, in uremia. Chart 3 (dog 6-22) illustrates this result, which is like that obtained from excessive constriction or occlusion of one

and Extrarenal Arteriolar Necrosis and Necrotizing Arteriolitis, in *Blood, Heart and Circulation*, Publication 13, American Association for the Advancement of Science, New York, Science Press Printing Company, 1940, p. 266.

15. Rodbard, S., and Katz, L. N.: The Role of Renal Metabolism in Hypertension and Uremia, *J. Exper. Med.* **73**:357 (March) 1941. Goldblatt and others.¹⁴ Goldblatt,^{2c} Katz and others.²¹

main renal artery with contralateral nephrectomy, and can be attributed to the absence of the compensating, neutralizing or inhibiting effect of a normal kidney.¹⁵

Comment.—On the basis of the preceding two series of experiments it can be stated that the failure of the blood pressure to become elevated in a dog with the main artery of one kidney constricted and the ureter of the same kidney occluded and with a contralateral normal kidney is not due to the absence of a pressor-producing substance from the venous blood of such a kidney. Direct evidence that a vasoconstrictor substance is actually present in the venous blood from the ischemic kidney with the ureter occluded and not in the venous blood from the normal kidney is supplied by the following experiments.

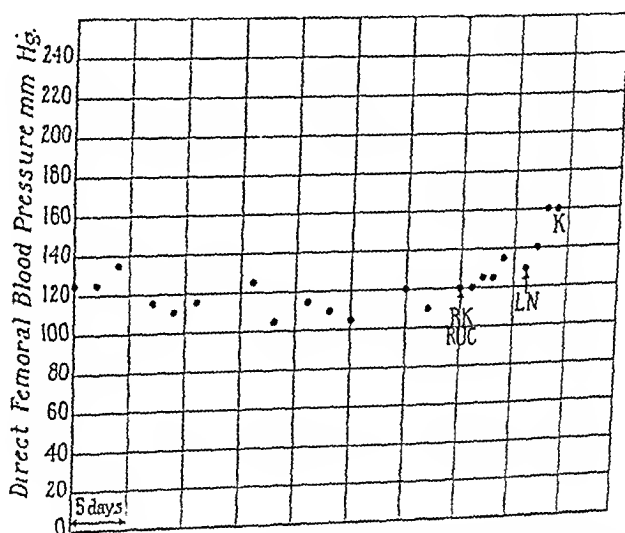


Chart 3 (dog 6-22).—Effect on blood pressure of constriction of the main artery and occlusion of ureter of one kidney followed by excision of the contralateral normal kidney. RK, moderate constriction of the right main renal artery. RUC, occlusion of the right artery. LN, left nephrectomy. K, killed.

Vasoconstrictor Property of Venous Blood Plasma from a Kidney with the Main Artery Constricted and the Ureter Occluded, Compared with Venous Blood Plasma from the Contralateral Normal Kidney and with Systemic Venous Blood Plasma.—In 9 dogs with the main renal artery constricted and the ureter occluded in which no rise of blood pressure had occurred in from five to ten days after the operation, the main vein of each kidney was cannulated and blood obtained for a test (Läwen-Trendelenburg technic) for vasoconstrictor substance in the citrated plasma. At the same time an additional control specimen of blood from the jugular vein was obtained for the test. The blood was obtained while the animal was under pentobarbital sodium anesthesia. The technic of the test was that described by Fasciolo, Houssay and Taquini.³⁷ The same final dilution of blood plasma in sodium citrate and Ringer's solution was employed. *Bufo peltacephalus*, a giant toad from Cuba, was used for the tests. The hind portion of the toad was first perfused through the abdominal aorta with 0.5 per cent sodium citrate in Ringer

solution from a Marriott bottle, and the outflow of drops from the abdominal vein was counted at intervals of five minutes until the rate of flow was constant. Then the fluid was changed abruptly to the citrated plasma to be tested, and the perfusion was continued for twenty-five minutes. Counts of the outflow were made at intervals of five minutes. The difference between the number of drops at the point of greatest change of flow and the number of drops at the constant level, expressed in per cent of the constant value, was regarded as the index of constriction or dilatation of the peripheral vessels in the perfused portion of the toad. Two 25 cc. samples of venous blood (for two separate tests) were usually obtained from each kidney, and as a rule only one sample of systemic blood was assayed. The plasma, diluted, 1 part in 7 parts of 0.5 per cent sodium citrate solution in Ringer's solution without calcium, was the final fluid tested. The rate of outflow of blood from the renal vein of the ischemic kidney was almost always slower than from the normal,

TABLE 3.—*Results of Comparative Tests*

Dog	Number of Days After Operation Samples of Venous Bloods Were Obtained	Degree of Constriction or Dilatation Produced by Plasma		
		From Venous Blood of Ischemic Kidney with Ureter Occluded	From Venous Blood of Normal Kidney	From Systemic Venous Blood
8-24.....	8	-83	- 7	+58
8-11*.....	6	-35 (left kidney) -80 (right kidney)	- 8
8-08.....	7	-50	+15	+41
8-09.....	7	-46	+40	+22
8-10.....	7	-32	-13	+10
8-26.....	7	-23	- 1	+72
8-07.....	6	- 7	0	+10
8-05.....	7	+ 7	+22	+70
8-06.....	4	+56	+130	+87

* In this animal the left main renal artery was first constricted and the left ureter cut. Two weeks later the same operations were performed on the right side. Both kidneys were therefore ischemic.

but the difference between the two rates varied, depending on the degree of constriction of the main renal artery.

The tests were all carried out objectively; the investigator who performed them did not know the source of the various specimens until the result was obtained. In table 3, which gives the results of the tests, the minus sign before the values indicates constriction and the plus sign dilatation. Although the degree of constriction effected by the venous blood from the kidneys with the renal artery constricted and the ureter occluded varied greatly, there was a significantly constrictive effect from the plasma of at least 6 of the 9 animals. On the contrary, the plasma from only one normal kidney produced some constriction, while that from the remainder showed no effect or a variable degree of dilatation. There was almost always a definite, though variable, dilator effect from the systemic venous blood plasma, although the latter has a greater viscosity than the control Ringer solution. In the case of dog 8-06 (table 3), the result was strikingly different from all others and may have been due to some undetected technical irregularity in the preparation of the toad, to some error in the preparation of the Ringer or the citrate solution or to inadequate constriction of the renal artery. A few experiments were performed which showed that the vasoconstrictor effect was not due to

epinephrine or tyramine, and the fact that the vasoconstrictor effect was not reversed by piperidomethyl-3-benzodioxane (933 F) indicates that the vasoconstrictor substance in the plasma was probably identical with that which has been found in the venous blood from kidneys with the main artery constricted and the ureter intact¹⁵ and which is now regarded as the humoral agent that produces renal hypertension.¹⁶

GENERAL COMMENT

This study is reported at this time because of the possible practical application of the results already obtained to the problem of the performance of unilateral nephrectomy for the treatment of hypertension in man when it is associated with unilateral renal disease. It is justifiable to suggest that if in cases of such association there is no output of urine from the diseased kidney, owing to occlusion of the ureter from any cause, the probability is great that the hypertension is due either to disease of the other kidney or to some other cause. Lowering of the blood pressure should not be expected, therefore, to result from excision of a completely nonfunctioning kidney whose lack of function is due to occlusion of the ureter, even though there is some indication that in man such a kidney may still be the source of a hypertensive effect. In such circumstances, for the present at least, nephrectomy is perhaps best performed only if the obviously diseased kidney is the source of other untoward clinical effects (infection or persistent pain, for example) for which removal of the kidney might in any event be indicated.

Several cases of unilateral nephrectomy for complete hydronephrosis in which a return of the elevated blood pressure to normal has occurred and has persisted for several months after the operation have been reported to us. In 1 of these cases the kidney showed such advanced destruction, with practically no tubules and only relatively few glomeruli left in the wall of the sac, that it is difficult to accept this as the source of the hypertensive effect. Yet for several months after the nephrectomy the blood pressure remained normal. At the Cleveland City Hospital, in the service of Dr. R. W. Scott, there was observed a case of unilateral chronic pyelonephritis, with the usual intrarenal vascular disease, in which before the operation no urine was obtained from the affected kidney and no indigo carmine was excreted by it, although the pelvis could be filled from below. The patient's systolic blood pressure was usually 200 mm. of mercury or more, and the diastolic 120 mm. or more, before the operation; yet within a day after the operation the blood pressure fell to 120 systolic and 80 diastolic, and it has remained within

16. Page, I. H.: Newer Aspects of Experimental Hypertension, in *Blood, Heart and Circulation*, Publication 13, American Association for the Advancement of Science, New York, Science Press Printing Company, 1940, p. 239. Blalock, A.: Experimental Hypertension, *Physiol. Rev.* 20:159 (April) 1940.

normal limits during a period of five weeks since the operation. On the day of the patient's discharge from the hospital the blood pressure was 108 systolic and 78 diastolic.

SUMMARY AND CONCLUSIONS

Constriction of one main renal artery in the dog causes a variable rise of blood pressure, which persists for a variable period. Excision of the ischemic kidney results in a prompt fall of the blood pressure to normal. Similarly, in man, hypertension may be associated with unilateral renal disease, presumably producing ischemia, and removal of the diseased kidney results in a fall of the blood pressure to normal if the other kidney is normal.

Occlusion of one ureter in the dog does not result in elevation of blood pressure. Occlusion of the ureter performed at the same time that the main artery of the same kidney is constricted interferes with the development of the elevated blood pressure of a dog with unilateral renal ischemia. After the blood pressure has become elevated owing to constriction of one main renal artery, occlusion of the ureter of the same kidney causes a fall of blood pressure to normal in from three to seven days. Constriction of both main renal arteries accompanied with occlusion of both ureters usually results in a moderate elevation of blood pressure, which persists until death of the animal in uremia. Occlusion of the ureter and constriction of the main artery of one kidney followed by contralateral nephrectomy also usually results in a moderate elevation of blood pressure, which persists until death occurs in uremia. A hypertensive effect is, therefore, produced by kidneys with the main artery constricted and the ureter occluded when no normal kidney is present.

A vasoconstrictor effect has been obtained (by the Lävén-Trendelenburg technic) with citrated plasma of the venous blood of kidneys with the renal artery constricted and the ureter occluded, although the blood pressure of the animals was not elevated. No vasoconstrictor effect, but rather a dilator effect, was obtained with the plasma of venous blood from the contralateral, normal kidney and of systemic venous blood. This indicates that the effect of occlusion of the ureter on a kidney with the main artery constricted is not to abolish the production of pressor substance but to interfere with the rate of entrance of pressor-producing substance from the kidney into the systemic circulation or diminish the amount produced. In either case, the failure of the blood pressure to become elevated as a result of the decreased amount of pressor-producing substance which enters the systemic circulation may also be due to the neutralizing effect of the contralateral normal kidney.

Although some human beings have already been described in whom excision of a kidney with the ureter completely obstructed or of a kidney from which no urine was obtained was followed by a return of the blood pressure to normal, the experiments indicate that this may not prove to be the rule and that in such cases excision of the kidney should be undertaken for the main purpose of removing the diseased organ rather than for possible cure of the hypertension. In all cases of contemplated unilateral nephrectomy it is desirable, with the limited means available at present, to determine that the other kidney is, as far as can be determined, normal, before removing an obviously diseased, though still functioning, kidney for the possible favorable effect of this procedure on the elevated blood pressure.

NAEVUS UNIUS LATERIS

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One of the most interesting and certainly the most unusual of the varieties of nevi is the so-called neuropathic papilloma, or naevus unius lateris. It is a papillary or verrucous congenital tumor having a unilateral or nearly unilateral distribution in linear streaks or bands following the long axis of the limbs or extending transversely around the trunk. This unique disease is so striking that it is readily recognized as a distinct clinicopathologic entity. Only 4 cases have been observed among 40,000 patients with tumors studied at the Memorial Hospital, an incidence of 0.01 per cent. To these have been added 156 cases from the literature, thus affording 160 cases for analysis.

SYNONYMS

The term naevus unius lateris was originated by von Baerensprung in 1863. Theories as to etiology, variations in appearance of the reported lesions and attempts to create names embodying both descriptive and pathogenetic elements have led to the appearance of a host of synonyms in the literature, of which the following are examples: naevus linearis unius lateralis, naevus verrucosus unius lateris, linear nevus, systematized nevus, naevus unilateralis, naevus lateralis, naevus verrucosus, naevus papillaris, naevus pigmentosus unius lateris, naevus nervosus, naevus papillaris neurosus, *naevus verruqueux unilateral*, *naevus verruqueux zoniformis*, *naevus lichenöide*, *naevus lichenöide k ratopilaire*, *naevus k ratosique syst matis *, naevus neuroticus, naevus linearis verrucosus, naevus linearis ichthyosiformis, naevus neurapathicus, verrucopapillomatosis, ichthyosis hystrix congenita, ichthyosis cornea, ichthyosis cornea (hystrix) partialis, ichthyosis linearis neuropathica, ichthyosis hystrix nigricans, ichthyosis linearis congenitalis, papilloma neuropathicum.

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From the Mixed Tumor Service, the Memorial Hospital for Cancer and Allied Diseases.

papilloma neuroticum, *papilloma corné neurotique*, papilloma essentielle neuropathicum, papilloma neuropathicum unilaterale, unilateral papilloma, *papillome eczématiformé*, eczema neuroticum, *keratose linéaire systématisée*, neurodermitis linearis chronica verrucosa, congenital neuropathic warts and congenital papillary streaks.

CRITERIA

Von Baerensprung¹ stated that this nevus is always unilateral and limited to the median line; that the areas affected correspond to the peripheral distribution of one or more nerves; that the subcutaneous changes consist in hypertrophy of the papillae—in which the nerves terminate—and that glands and hairs take no part in the development of the lesion.

Morrow² concluded that the expression "linear naevus" is adequate. He stated the belief that all the lesions present certain objective characteristics sufficiently similar to justify their inclusion in the same category. The more typical of these characteristics are:

1. There is linear distribution, following the long axis of the limb or directed transversely on the trunk.
2. The distribution is unilateral.
3. The nevus is papillary or verrucous.
4. The origin is congenital, the nevus commonly appearing at birth or in the first few months of life but occasionally during adolescence or later.
5. Sensory disturbances are often a marked feature but may be entirely absent.
6. The nevus may increase in extent, remain stationary, spontaneously retrogress or undergo various degenerative changes (exceptionally malignant transformation).

Heidingsfeld³ agreed with Morrow's criteria and expressed the belief that three or four of these characteristics are enough for diagnosis. Adamson,⁴ however, stated the opinion that the verrucous type of nevus is not the only form and that the growth may involve any element of the

1. von Baerensprung: *Naevus unius lateris*, *Charité-Ann.* **11**:91, 1863.

2. Morrow, P. A.: Two Cases of Linear Naevus, with Remarks on Its Nature and Nomenclature, *New York M. J.* **67**:1, 1898.

3. Heidingsfeld, M. L.: *Linear Naevi*, *J. A. M. A.* **43**:597 (Aug. 27) 1904.

4. Adamson, H. G.: Some Remarks on Zoniiform or Segmented Naevi, *Brit. J. Dermat.* **26**:379, 1914.

skin, a point which Étienne⁵ had previously made. Meissner⁶ pointed out three characteristics common to this type of nevus:

1. Congenital origin, the lesion appearing at birth, early in childhood, during pregnancy or in the puerperium.
2. Failure to pass the midline.
3. Absence of deleterious effect on vital processes or general health.

ETIOLOGY

Many theories as to the cause of this nevus have been conceived, and objections have been made to all of them. Von Baerensprung¹ expressed the belief that the site of the disease is in the spinal ganglions and that the distribution of the nevi coincides with the extension of the cutaneous nerves. This theory, or modifications of it, has had many adherents. Hyde,⁷ Mackenzie,⁸ Kudisch⁹ and Plonski¹⁰ agreed that intrauterine disease of the spinal ganglions causing persistent trophic disturbance is the probable cause. Gerhardt¹¹ concluded that the nevus is the result of disease affecting the central nervous system, a view later shared by Reckzeh¹² and Lewith.¹³ Müller¹⁴ concluded that the lesions correspond more to central than to peripheral nerves. Spietschka¹⁵ saw significance in the fact that in some cases the patients showed nervous disturbances. Hagen¹⁶ expressed the belief that congenital diseases of the skin with

5. Étienne, G.: Naevi dans leurs rapports avec les territoires nerveux; essai de pathogénie et d'étiologie, *Nouv. iconog. de la Salpêtrière* 10:263, 1897; abstracted, *Brit. J. Dermat.* 10:28, 1898.

6. Meissner, P.: Ueber Naevus verrucosus, *Dermat. Ztschr.* 2:478, 1894-1895; abstracted, *Brit. J. Dermat.* 8:407, 1896.

7. Hyde, J. N.: Rare Form of Congenital, Multiple and Monolateral Pigmentary Naevus, Having the Disposition of Zoster Corporis, *Chicago M. J. & Examiner* 35:377, 1877.

8. Mackenzie, S.: Papillary Growths of Nervous Distribution, *M. Times & Gaz.* 1:451, 1880.

9. Kudisch: Naevus Pigmentosus unius lateris, *Monatsh. f. prakt. Dermat.* 50:173, 1910.

10. Plonski: Ueber Naevus verrucosus, *Dermat. Ztschr.* 10:390, 1903.

11. Gerhardt, C.: Beobachtungen über neuropathisches Hautpapillom, *Jahrb. f. Kinderh.* 4:270, 1871.

12. Reckzeh: Naevus verrucosus pigmentosus unius lateris, *Med. Welt* 8:1406, 1934.

13. Lewith, R.: Ueber systematisierte Naevi und "naevusartige" Dermatosen, *Arch. f. Dermat. u. Syph.* 169:582, 1934.

14. Müller, J.: Ein Fall von Naevus verrucosus unius lateris, *Arch. f. Dermat. u. Syph.* 24:21, 1892.

15. Spietschka, T.: Ueber sogenannte Nerven-Naevi, *Arch. f. Dermat. u. Syph.* 27:27, 1894.

16. Hagen, A.: Zur Kenntniss des halbseitigen Naevus verrucosus, *München. med. Wchenschr.* 39:329, 1892.

disturbances of the central nervous system are due to deep-lying abnormal processes causing both. Nicolas, Rousset and Colas¹⁷ concluded that the coincidence of cutaneous lesions and skeletal malformations is in favor of the neural theory. Lewin,¹⁸ however, in reviewing 100 cases of this type of nevus found that in only 40 cases was the correspondence of the lesions to nerve distribution sufficient to suggest a neural influence.

Because of this discrepancy in many cases, Philippson¹⁹ explained the distribution of systematized nevi as determined by the lines of Voigt, i. e., the boundaries of the areas of distribution of the main cutaneous nerve stems. This theory was also brought forth by Hallopeau.²⁰

Blaschko²¹ assumed disturbed development of the epidermis in the embryo at the margin of a segment of skin, which might later involve the entire segment by surface extension of cornified epithelial ridges running in the same directions as cleavage lines of the skin and hair streams and that later in life the lines of the nevus might be influenced by irregular growth or by body movements. Jadassohn²² expressed agreement with direction of hair streams. Okamura²³ agreed with Blaschko and Jadassohn concerning hair streams and concluded that the lesion is caused by hypertrophy of the ectoderm due to changes in the mesoderm.

Kopp²⁴ connected the configuration of nevi with vascular distribution. Heller²⁵ is cited as the first to consider the dependence of systematized nevi on the lymphatic system, and Meissner⁶ expressed the belief that

17. Nicolas, J.; Rousset, J., and Colas, J.: Naevi verruqueux hyperkératosiques systématisés zoniformes à disposition unilatérales, *Bull. Soc. franç. de dermat. et syph.* **43**:819, 1936.

18. Lewin, in discussion on Meissner: Ueber Naevus verrucosus unius lateris, *Arch. f. Dermat. u. Syph.* **33**:204, 1895.

19. Philippson, L.: Zwei Fälle von Ichthyosis cornea (hystrix) partialis (Naevus linearis verrucosus, Unna), entsprechend dem Verlaufe der Grenzlinien von Voigt, *Monatsh. f. prakt. Dermat.* **11**:337, 1890.

20. Hallopeau, cited by Bohac.³¹

21. Blaschko, A.: Bemerkungen zu vorstehenden Aufsatz (Alexander), *Dermat. Ztschr.* **2**:361, 1895.

22. Jadassohn, J.: (a) Beiträge zur Kenntnis der Naevi, *Vrtljschr. f. Dermat. u. Syph.* **15**:917, 1888; (b) Zur Kenntnis der systematisierten Naevi: II. Bemerkungen zur Histologie der systematisierten Naevi und über "Talgdrüsen-Naevi," *ibid.* **33**:355, 1895; (c) III. Zur Lokalisation der systematisierten Naevi, *ibid.* **33**:373, 1895.

23. Okamura, T.: Zur Kenntnis der "systematisierten Naevi" und ihres Ursprungs, *Arch. f. Dermat. u. Syph.* **56**:351, 1901.

24. Kopp, C.: Zur Kasuistik des Naevus vasculosus verrucosus faciei (Darier), *Deutsches Arch. f. klin. Med.* **84**:135, 1905.

25. Heller, cited by Schmidt, O.: Betrachtungen über einen ungewöhnlich ausgebreiteten und morphologisch heterogenen Fall von systematisiertem Genetalnaevus, *Inaug. Dissert., Göttingen*, 1934.

warty nevi may be secondary to lymphangiectasis. This theory was viewed favorably by Adamson.⁴ Virchow²⁶ stated that vascular nevi occur in certain linear arrangements due to disturbance of closing of fissures in fetal life, a view which was later taken by Hasselmann²⁷ in regard to verrucous nevi.

Lindenheim²⁸ expressed the belief that there is a definite metameral relation to the distribution of nevi. Konzert²⁹ attributed nevi to segmental change in embryonic life, with the change in the central nervous system due to involvement of the ectoderm. It was the conclusion of Batut³⁰ and Bohac³¹ that the lesions can be explained on the basis of ectodermal changes without bringing nerves into consideration.

Montgomery³² in 1901 discussed the most prominent theories: 1. The lines follow the course of cutaneous nerves. 2. The lines run along Voigt's lines. 3. The lines follow lines of cleavage of the skin. 4. The lines follow the course of blood vessels. 5. The lines run in metameres or segments of the body. 6. The lines lie along embryonic sutures and follow the trend of growth of the tissues. He stated that the first theory is inadequate because the lesions often do not follow the same nerve throughout their extent. Similarly, as to the second theory, they often cross Voigt's lines. There are likewise many exceptions to the third theory, and the fourth was never long entertained. The fifth does not explain the lesions running up and down the back in the median line. Montgomery stated that the last theory most nearly fills all requirements. The nevus originates at an early stage of development of the fetus, when embryonic layers are still a plastic mass. The disturbing agent, whatever its nature, usually affects what will later become the papillary layer of the skin and usually falls on one or the other side of the midline. Afterward, with the closing of sutures, cells may be pulled one way or the other. Groups of cells become stretched along the line and follow the twists and turns. His objections to the theory were that

26. Virchow, R., cited by Schmidt, O.: *Betrachtungen über einen ungewöhnlich ausgebreiteten und morphologisch heterogenen Fall von systematisierten Geweb-naevus*, Inaug. Dissert., Göttingen, 1934.

27. Hasselmann, C. M.: *Naevus Pigmentosus Verrucosus Unilateralis: The First Case in a Filipino*, Jap. J. Dermat. & Urol. **35**:611, 1934; abstracted, Arch. Dermat. & Syph. **31**:398 (March) 1935.

28. Lindenheim, H.: *Zur Kenntnis der systematisierten Naevi*, Dermat. Ztschr. **24**:144, 1917.

29. Konzert, R.: *Zur klinischen und anatomischen Kenntnis der systematisierten Naevi*, Dermat. Wchnschr. **74**:1051, 1924.

30. Batut: *Des naevi systematisés*, J. d. mal. cutan. et syph. **16**:414, 1904.

31. Bohac, C.: *Beitrag zur Kenntnis des Naevus ichthyosiformis*, Dermat. Ztschr. **14**:535, 1907.

32. Montgomery, D. W.: *The Cause of Streaks in Linear Naevus*, J. Cutan. & Genito-Urin. Dis. **19**:455, 1901.

it premises longitudinal growth of transverse lesions; also, if streaking is due to stretching of a group of lesions, it should become attenuated, but it actually does not.

REPORT OF CASES

CASE 1.—A. V., a white American-born girl, was first seen at the Memorial Hospital on June 19, 1929, at the age of 13, because of an extensive pigmented verrucous and papillary nevus involving the left side of the body.

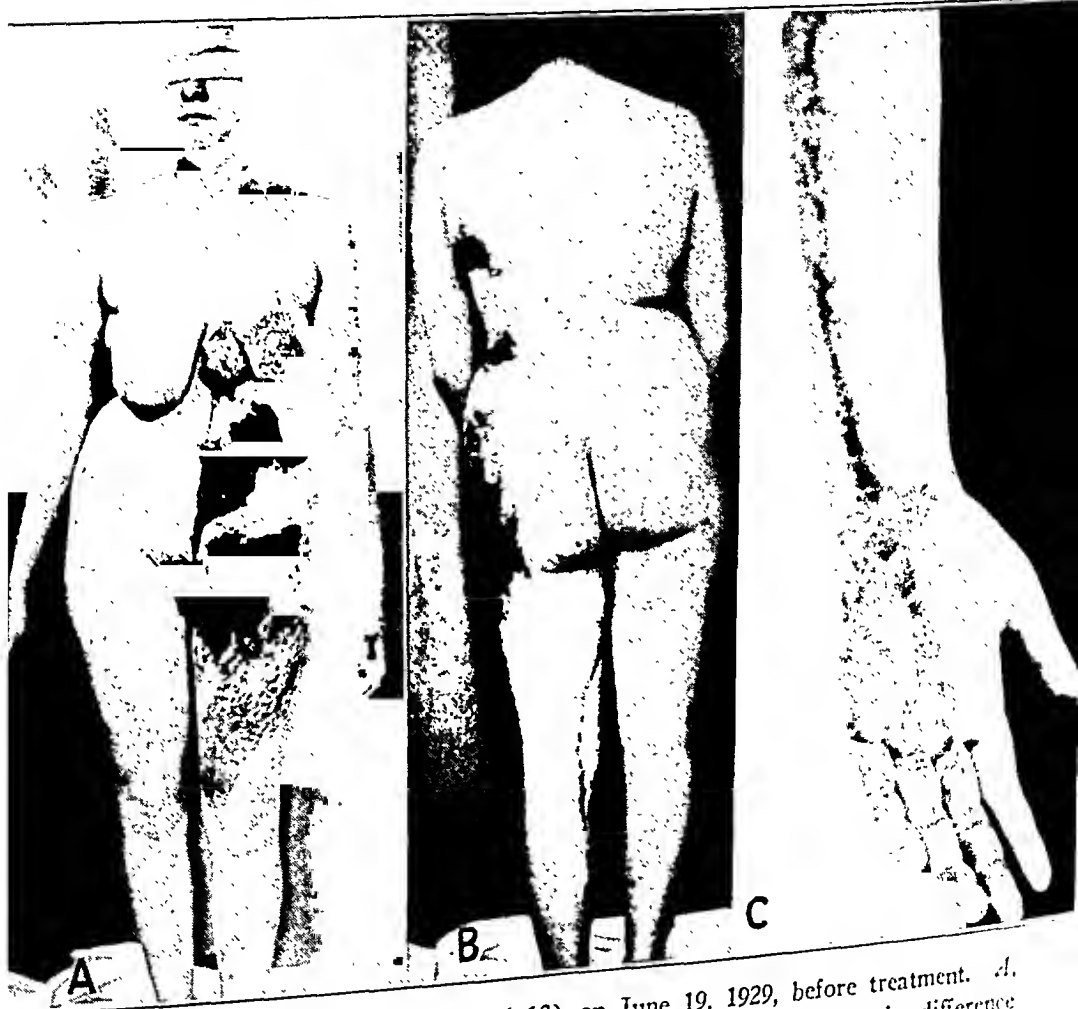


Fig. 1 (case 1).—Patient (aged 13) on June 19, 1929, before treatment. *A*, anterior view showing the distribution of the naevus unius lateris, the difference in the size of the breasts and the fungiform, papillary tumors in the umbilical and intermammary regions. *B*, posterior view, showing the distribution of the nevus on the trunk, left thigh and leg. *C*, arrangement of the nevus on the left forearm and hand.

Immediately after birth the mother noticed the lesions involving the left side of the body. She stated the belief that they were as extensive then as at the time of admission. Menstruation began at the age of 11, with normal menses.

periods. At the same time the breasts developed, but the right breast became more prominent than the left, and at the time of the girl's first appearance at the hospital it was 50 per cent larger. Three or four months before presentation a tumor mass formed between the breasts; it was painful and grew fairly rapidly.

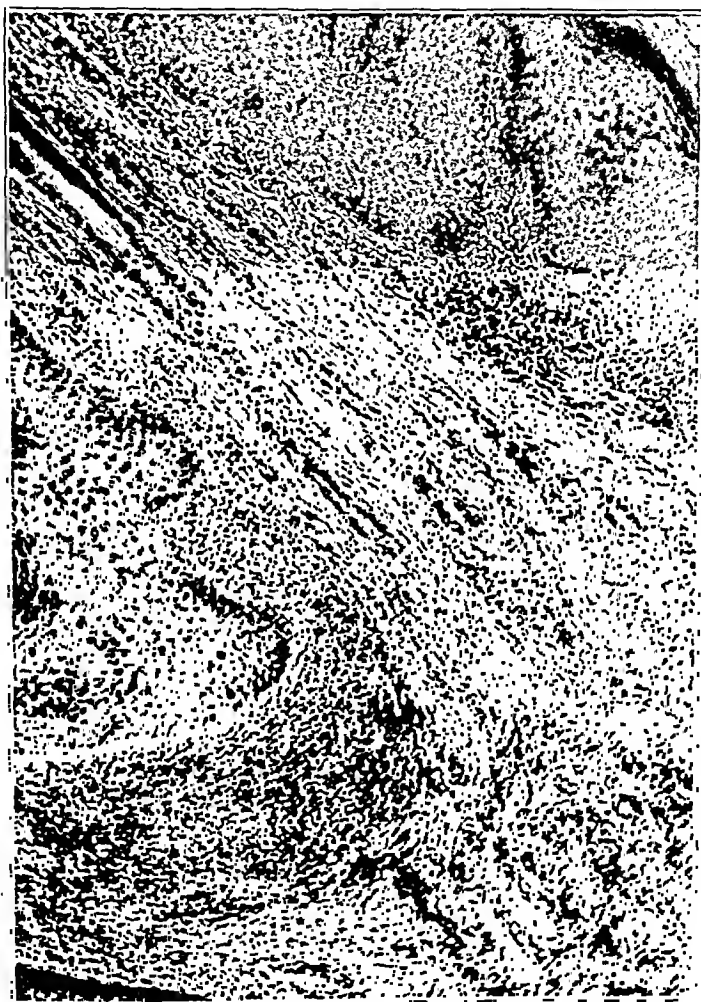


Fig. 2 (case 1).—Photomicrograph of a papillary tumor removed from the intermammary region on July 10, 1929, showing dense plasma cell infiltration of the corium. Medium power magnification.

Physical examination showed the patient to be healthy, overdeveloped and of normal mentality. She had no physical abnormalities other than the cutaneous lesion. The papillomatous, warty growth was arranged in large patches and streaks, confined entirely to the left side of the body and sharply limited by the

median line anteriorly (fig. 1). On the abdomen a line extended vertically from the xiphoid to the mons veneris but did not involve the vulva. From this line, below the umbilicus, there extended upward and to the left a roughly trapezoid solid patch. Just below the breast, a broad, densely covered band curved posteriorly from this mass over the iliac crest, with the concavity upward, and terminated just below the posterior superior iliac spine. Another closely covered patch extended from the lateral aspect of the pubis over the lower part of the abdomen, the inguinal region and the anterior and medial aspects of the upper part of the thigh. From the upper medial portion of the thigh a line of verrucous

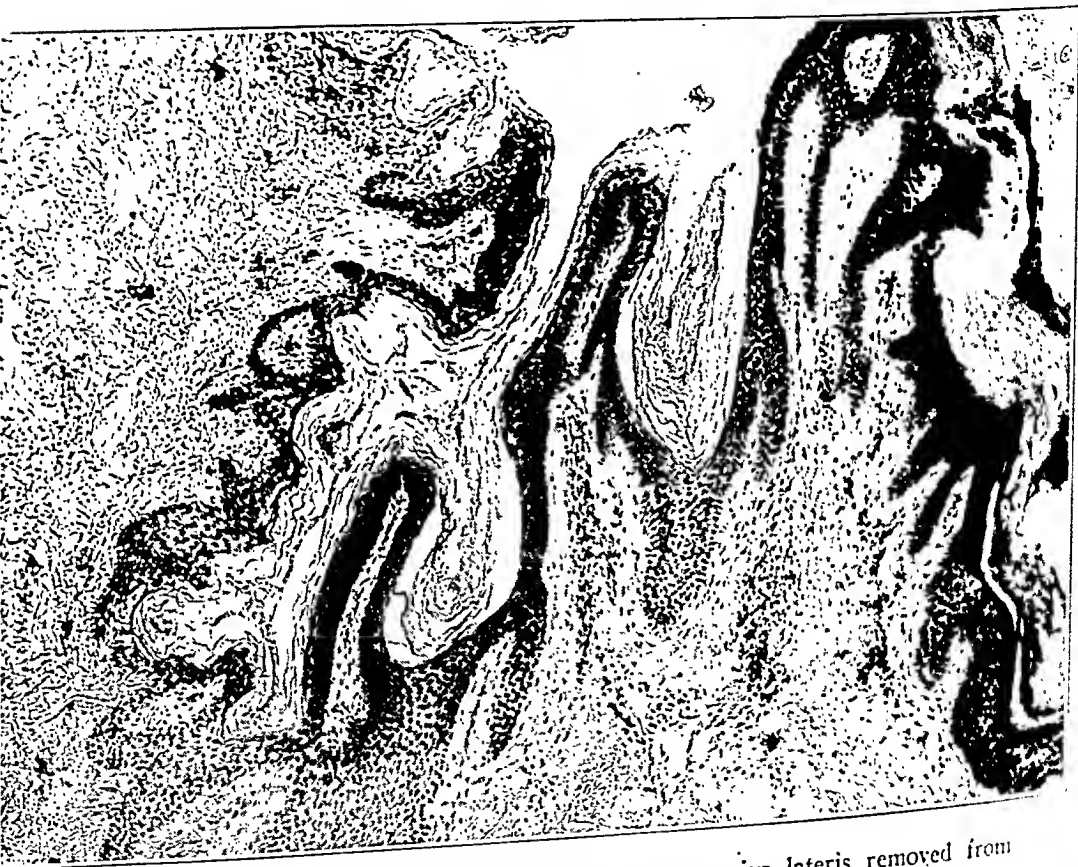


Fig. 3 (case 1).—Photomicrograph of a naevus unius lateris removed from the back on July 11, 1930. Marked hyperkeratosis, distortion and variations in thickness of the epithelial layer can be seen, as well as elongation of the papillae. Some groups of cells suggestive of "nevus cells" are seen in the corium, but these cells as a rule are never conspicuously present in this type of nevus.

lesions extended down the posteromedial aspect of the thigh, the popliteal region and the calf, to terminate in a scattered patch on the medial aspect of the middle third of the leg. The left breast was covered by small patches and small discrete nevi with intervening areas of normal skin. The areola and the nipple were involved. From the lateral aspect of the breast a dense patch extended into the axilla and was continued posteriorly as a horizontal band which ended just lateral

to the lower angle of the scapula. On the flexor surface of the left forearm, beginning just below the elbow, a line consisting of irregular small patches of warts curved down to the anteromedial aspect of the wrist, where it spread out to extend in two irregular patches across the medial aspect of the palm, involving the entire volar aspect of the fourth and fifth fingers and the anteromedial aspect of the third finger. At the upper extremity of the vertical abdominal line, between the breasts, was a fungating, mound-shaped, papillary, cauliflower-like tumor mass measuring 10 cm. in diameter at the base and elevated about 6 cm.

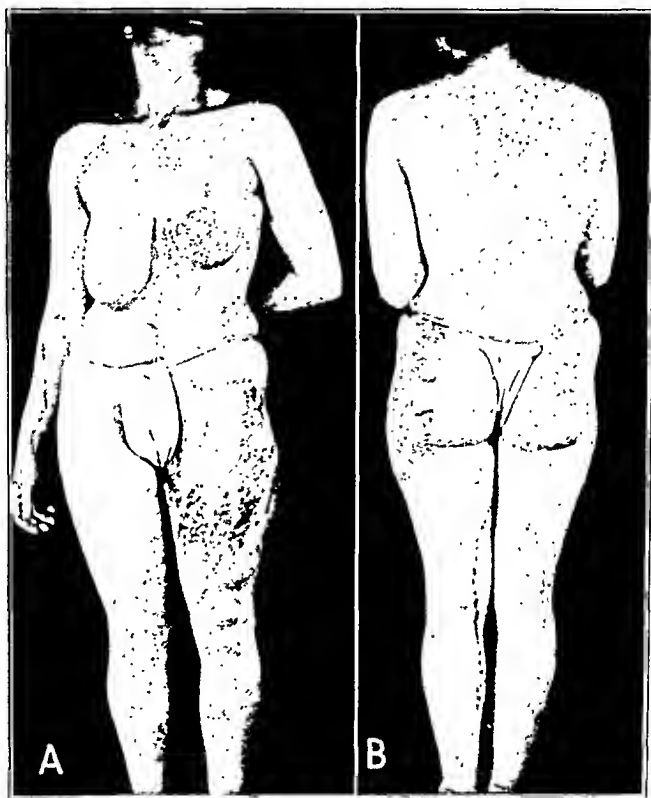


Fig. 4 (case 1).—Result of multiple stage excisions (June 17, 1936). *A*, anterior view, revealing scars and skin grafts following partial excisions of the nevus. *B*, posterior view, revealing minimal scarring on the left side of the back following excisions and plastic closures.

The patient was given two low voltage roentgen ray treatments (June 24 and 27) to the mass between the breasts, and on July 10 the mass was widely excised. Microscopic examination of the specimens showed only papillary nevus with marked secondary inflammation (fig. 2). On August 7 the abdominal nevus, together with

a margin of surrounding normal skin, was excised with the endotherm knife. The area granulated well, and on September 4 Thiersch grafts and a few Reverdin grafts were applied to the abdominal wound.

On July 10, 1930, the girl was readmitted to the hospital. On the following day the two nevi on the posterolateral aspects of the chest and flank were removed by



Fig. 5 (case 1).—Photomicrograph of a nevus removed from the medial aspect of the thigh on June 18, 1936, revealing the hyperkeratotic, papillary character of the tumor. Low power magnification.

sharp dissection (fig. 3). Elliptic incisions were made and closed by primary suture. By November 10 she had three ulcerations on the left breast, which continued for two months. On Jan. 23, 1931, she was given two roentgen ray treat-

ments to the left breast, with marked improvement. Another roentgen treatment was given to the breast September 14, with subsequent improvement.

On April 5, 1932, the patient was again admitted to the hospital but refused operation and was discharged two days later. As the thigh showed late improvement in response to roentgen therapy, she was given two more treatments (July 28 and September 15). There was disappearance of numerous growths, but on November 28 there developed a radiation ulcer in the skin of the thigh, which persisted and increased to 8 cm. in diameter.

She was admitted to the hospital for the fourth time on Jan. 11, 1933, and an excision of the ulcer and the surrounding nevus was performed. On February 2, Reverdin grafts were applied. By this time the nevus had been for the most part obliterated or excised, the only remaining areas of pronounced growth being on the medial and lateral aspects of the thigh. Although further excision was urged,



Fig. 6 (case 1).—Ulcerated carcinoma of the left breast (March 20, 1939) in a patient who had a naevus unius lateris.

the patient refused until June 17, 1936, when she again entered the hospital. The result of the treatment up to this date is shown in figure 4. The following day a long patch of the tumor was excised from the medial aspect of the thigh (fig. 5). She was discharged on July 17.

After this hospitalization the patient would not return to the clinic for three years. When next seen (March 20, 1939), she complained of swelling of the left breast, with increased heat and hardening of the skin. Examination showed most of the breast to be involved by a hard ulcerated tumor mass, which had invaded the skin (fig. 6). There were large hard nodes in the left axilla. Aspiration biopsy showed mammary carcinoma. Roentgen study of the chest at that time did not show metastasis; so a wide radical mastectomy was performed on March 31. A cutaneous defect was left in the central portion of the incision and was later repaired by graft-

ing, with satisfactory healing. Microscopic study showed infiltrating mammary carcinoma grade II (fig. 7), with metastatic carcinoma in the axillary nodes. On April 10 a roentgenogram showed pulmonary metastases. The patient was discharged on April 20 and died at her home on June 9, at the age of 23.

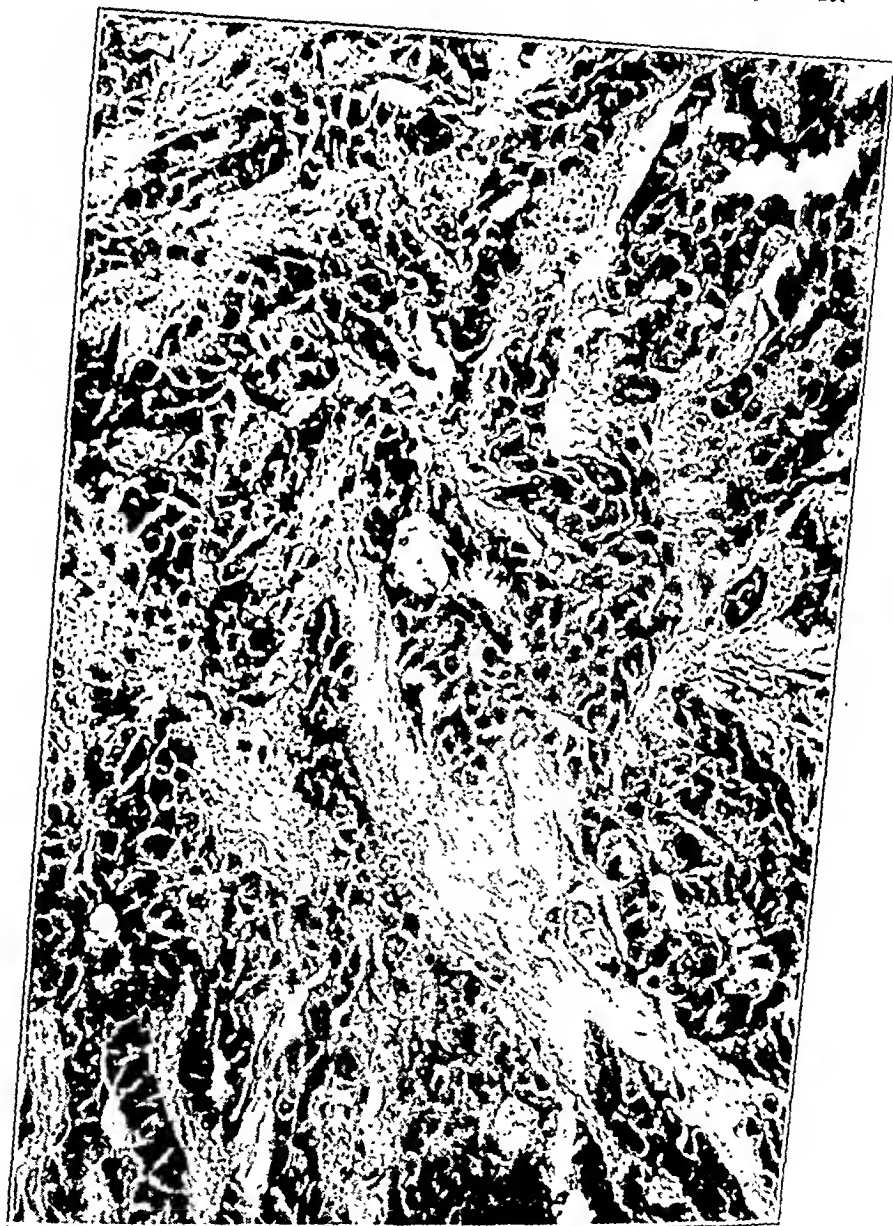


Fig. 7 (case 1).—Photomicrograph of the mammary carcinoma shown in figure 6.

CASE 2.—E. L., a white, American-born 39 year old man, first presented himself at the Paterson General Hospital on Dec. 9, 1933. He had a papillary pigmented nevus distributed on the right side of the chest and the right arm.

Since birth the patient had presented a pigmented horny nevus on the skin of the right side of the chest wall and the right arm, with a few isolated lesions on the

forearm and hand. The growth had always been confined to the right side of the body and had not changed in extent. There had generally been a foul-smelling watery discharge from several regions of the nevus, and occasionally bleeding occurred when the surface was cleaned.

On his first appearance at the hospital physical examination showed an excellent general condition, there being no abnormality other than the presenting cutaneous lesion. This was a papillary, warty dark brown nevus limited to the right side of the body. The individual lesions were arranged in large plaques, broad bands and occasional smaller patches and streaks (fig. 8).

Sharply demarcated at the midline anteriorly, extending above and below the xiphoid process, was a plaque which terminated inferiorly in a finger-like projection



Fig. 8 (case 2).—Photographs taken Dec. 14, 1933, before treatment. *A*, anterior view, showing a naevus unius lateris of the chest, axilla, arm, forearm and hand. *B*, posterolateral view.

extending vertically downward just to the right of the median line. Laterally this plaque split into two bands, the lower of which extended horizontally around the chest and at the posterior axillary line expanded to form a large, somewhat ovoid patch with irregular margins and terminated in the midclavicular line posteriorly. The upper band extended a short distance laterally and upward, joined a broad band which extended laterally just below the axilla and ended at the lower angle of the scapula. This in turn joined an irregular patch occupying the medial aspect of the upper third of the right arm. On the hypothenar eminence and the

medial aspect of the wrist was another irregular patch, and there was a streak of lesions on the dorsal aspect of the terminal two phalanges of the fifth finger.

Treatment of the nevus consisted of surgical excision in five stages. The first four operations were performed at the Paterson General Hospital (December 16; Jan. 27, 1934; March 17, and April 7). In this series of operations the portions of the nevus occupying the chest wall and the axilla were removed. In the first three operations primary wound closure was carried out, but after the fourth operation Reverdin skin grafting was performed.

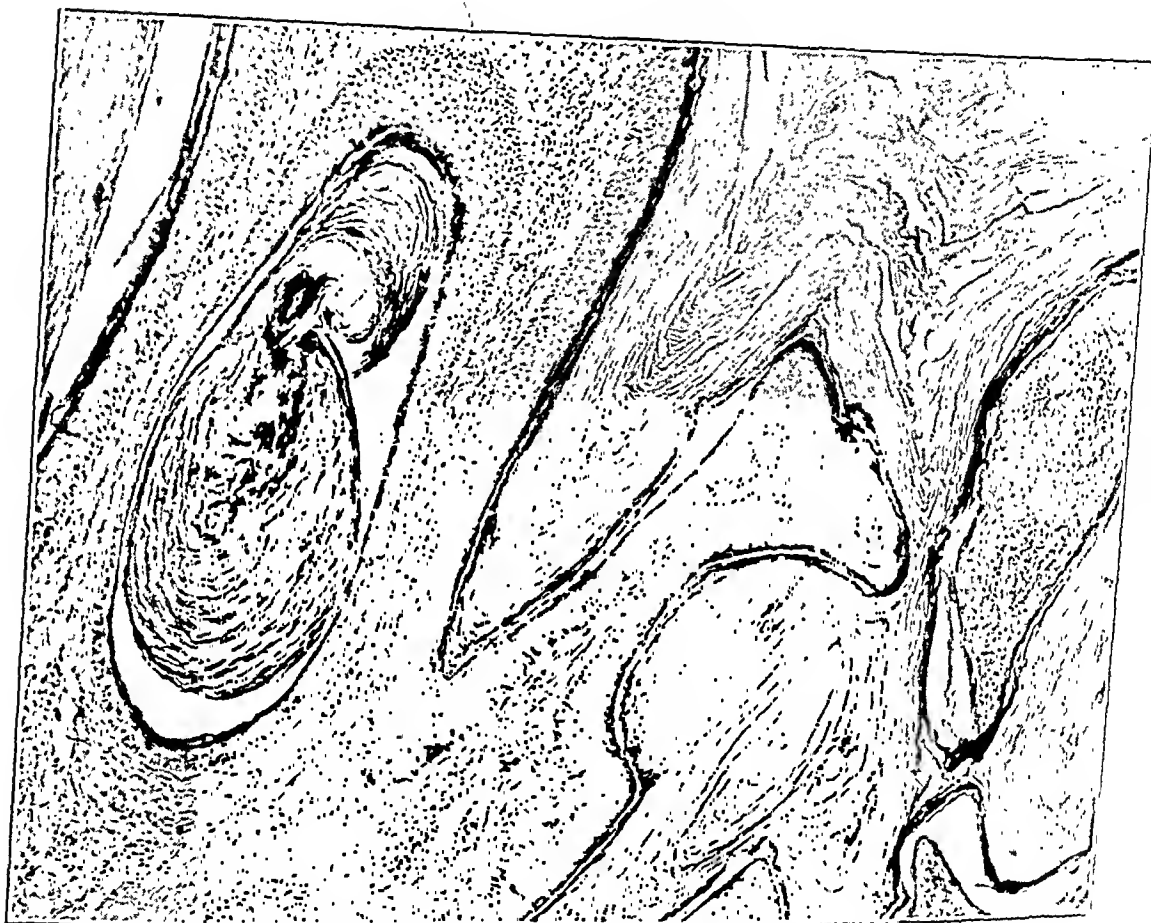


Fig. 9 (case 2).—Photomicrograph of a naevus unius lateris removed from the arm on Aug. 23, 1934, showing hyperkeratosis and distortion of the epithelial layers and papillae.

On August 23, at the Memorial Hospital, the remaining nevus on the arm was excised (fig. 9) and covered with Thiersch grafts, all of which took satisfactorily. This completed the removal of the growth (fig. 10), and the patient was observed at both the Paterson General Hospital and the Memorial Hospital at frequent intervals. There was no recurrence of the nevus.

After August 26 he was not seen until Jan. 27, 1937, when he appeared at the Paterson General Hospital, complaining of vomiting after meals for one week.

Fluoroscopic study after administration of barium sulfate revealed an obstructive lesion in the lower terminal portion of the esophagus. Removal of a biopsy specimen through an esophagoscope showed epidermoid carcinoma. Gastrostomy and a blood transfusion were done on February 1, and a series of roentgen treatments to the esophagus was instituted. However, on February 20 thrombosis of the right iliac artery occurred. The patient became rapidly weaker and died the following day, February 21.

A restricted postmortem examination showed the carcinoma also to involve the cardia and the greater curvature of the stomach, and there were metastases to the lymph nodes in the gastrohepatic ligament and to those about the pancreas.

CASE 3.—G. P. M., a 36 year old American-born white married man, was admitted to the Memorial Hospital on Nov. 6, 1932.

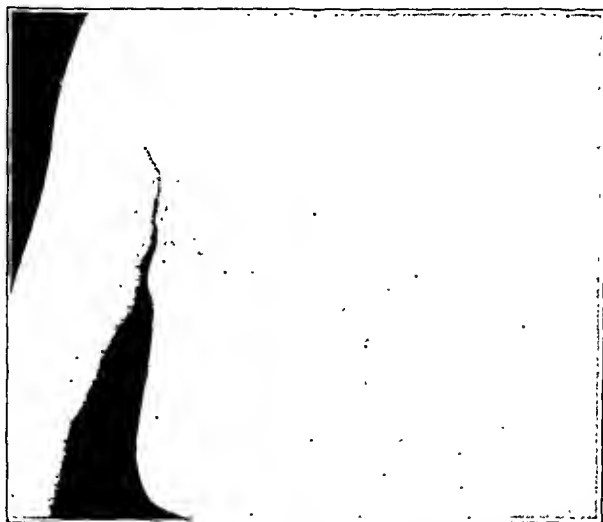


Fig. 10 (case 2).—Slight scarring after complete removal of the nevus in multiple stages (Sept. 26, 1934).

Since birth this patient had had a pigmented papillary nevus involving the right side of the trunk and the right upper extremity. The nevus caused no symptoms apart from bleeding on slight trauma, and there was no change in its appearance or extent until the spring of 1932, when several small areas on the shoulder and arm seemed to grow larger. On September 15 the patient noticed a small lump in the right axilla. Ten days later he began to suffer severe pain in this region. He also had sharp pain in the right side of the chest on coughing or sneezing. There was no hemoptysis, but he became dyspneic.

On October 26, in Pittsburgh, lymph nodes were removed from the right axilla. Dr. Ewing examined the specimen microscopically and made a diagnosis of metastatic epidermoid carcinoma.

Physical examination on admission to the Memorial Hospital on November 6 showed the right side of the shoulder girdle to be noticeably smaller than the left, and the right nipple was atrophied and retracted upward and outward. In the right

axilla was a recently healed surgical incision. Beneath this scar there was marked induration of the subcutaneous tissues and several hard nodes could be palpated. There was considerable telangiectasia of the skin of the right axilla from previous irradiation.

Limited for the most part to the right side of the body was a dark brown pigmented, papillary nevus. It was distributed on the trunk and upper extremity (fig. 11). From the sternal notch to the level of the nipple a vertical band extended down the median line, which sharply limited its left border. From the sternal notch the area spread laterally over the right clavicular region onto the anterior and superior aspects of the shoulder, which it covered in a capelike fashion. This area extended down anteriorly into the axilla and just above the nipple gave

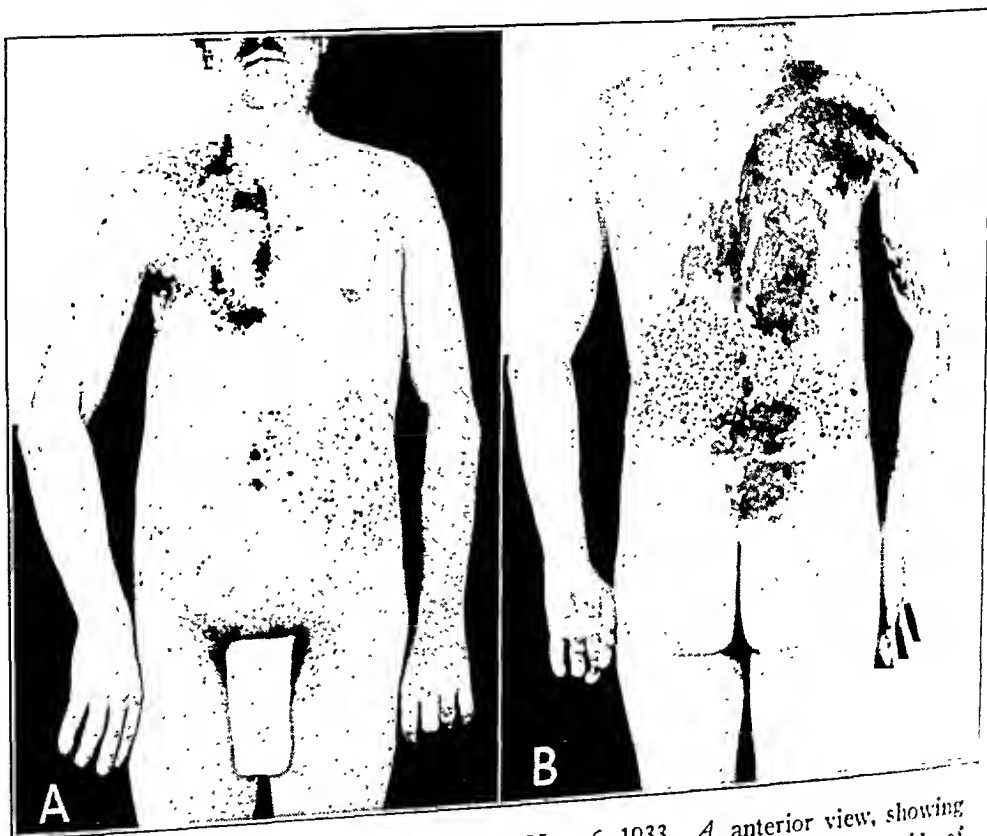


Fig. 11 (case 3).—Photographs taken Nov. 6, 1933. *A*, anterior view, showing the distribution of the naevus unius lateris. Note the atrophy of the right side of the shoulder girdle. *B*, posterior view. The site of malignant degeneration of the nevus cannot be seen in either view.

off a broad band, which passed downward and medially to terminate just to the right of the xiphoid process.

On the posterior aspect of the trunk the lesions extended a short distance to the left of the midline in the lumbar and interscapular regions. Largely covering the thoracic region and on the posterior aspect of the shoulder were several irregular patches, the upper portion of which joined the previously described area on the superior aspect of the shoulder. Irregular, continuous and interrupted streaks extended down all surfaces of the arm to the elbow, and a few streaks extended down the medial surface to the midpoint of the forearm.

In the upper part of the lumbar region posteriorly there was a broad band of skin which showed slightly increased pigmentation and in which were small, sparsely scattered lesions. There were also smaller similar areas in both groins. On the posterior and medial aspects of the right arm and in the right supra-clavicular region were four small growths, which were firmer, more granular and suspected of being neoplastic.

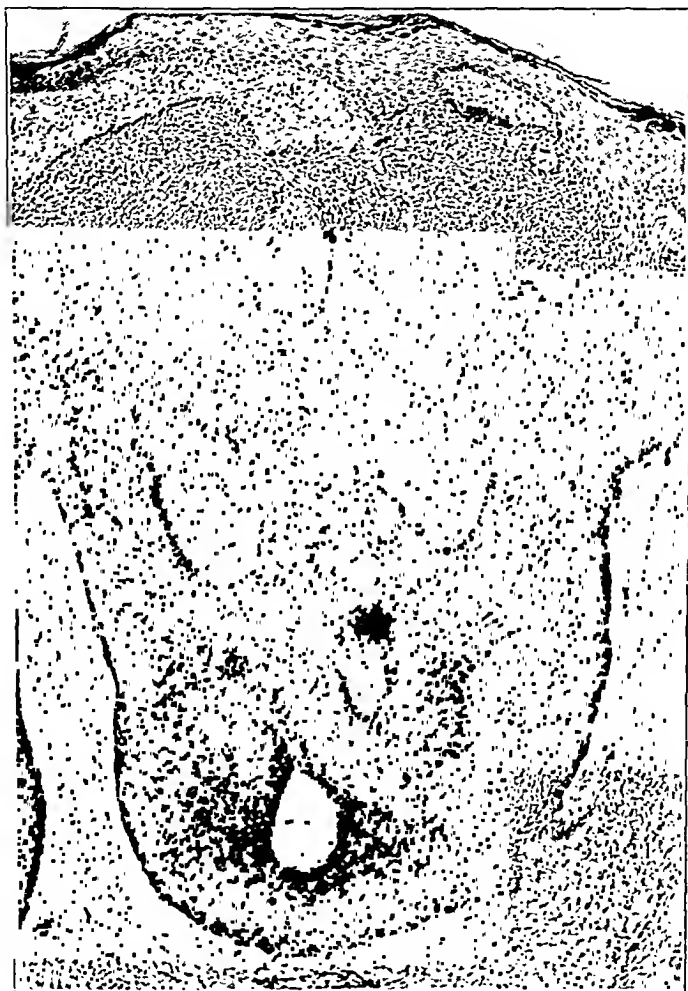


Fig. 12 (case 3).—Photomicrograph of a nodule of recent development in a naevus unius lateris. The lesion is a typical basal cell carcinoma. The malignant tumor derivative of the naevus unius lateris is usually either a basal cell or a squamous cell carcinoma, practically never a melanoma.

Roentgen examination of the chest on entry showed multiple spherical opacities in the lungs, interpreted as metastases.

Biopsy of the aforementioned nodules in the skin was done on November 7. At the same time the axilla was exposed. The entire axilla was so densely

fibrotic that further exploration was not done. Microscopic examination of each of the four cutaneous nodules excised revealed pigmented basal cell epithelioma with adenoid features (fig. 12).

The patient was started on a course of low voltage roentgen therapy, but this had to be abandoned because of pain in the axilla and inability to lie on the table. He returned to his home on December 6 and died there on December 27. The location of the primary epidermoid carcinoma in the skin, which had metastasized to the axillary lymph nodes and to the lungs, was not found.

CASE 4.—H. C., a 24 year old American-born white man, came under observation at the Memorial Hospital on only one occasion, May 19, 1937, and never received treatment in any form.

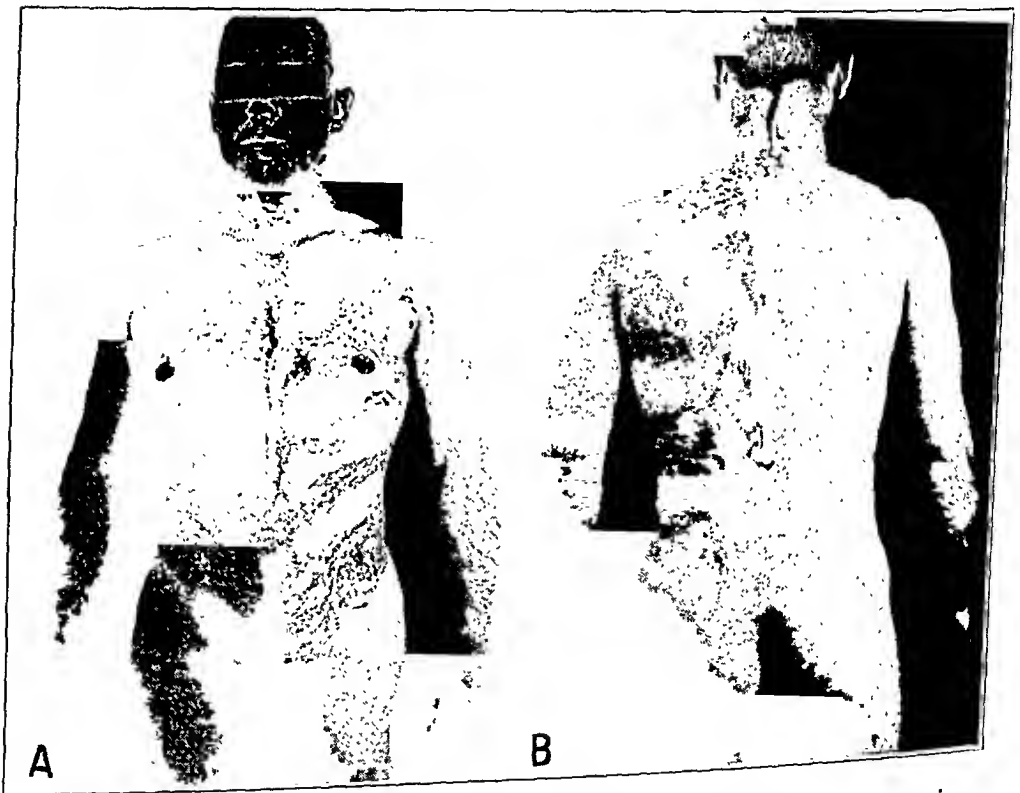


Fig. 13 (case 4).—Photographs taken May 19, 1937. *A*, anterior view, showing the bilateral distribution of the nevus in the neck and the submental region. The tumor in the left temporal region can also be seen. *B*, posterior view.

Since birth there had been an extensive pigmented nevus on the left side of the body, which had never caused any symptoms and had not increased in area.

Physical examination showed a pigmented brown verrucous nevus sharply limited to the right side of the body except on the anterior aspect of the neck, where it was bilateral (fig. 13).

Beginning in the midsternal line was a vertical neval streak which extended downward in the median line, running an interrupted course and dwindling out midway between the xiphoid process and the umbilicus. Covering the umbilicus

was a rosette of papillary lesions, and from there a solid line of nevi extended down to the pubis.

Between the level of the left inguinal ligament and the left pectoral region was a series of four bands of lesions. Each band was composed of individual streaks and patches between which were areas of unaffected skin. These bands began at the midline and swept laterally and upward around the body to terminate posteriorly in irregular patches which came within 5 cm. of the median line. The lower band terminated at a level of the crest of the ilium. The middle bands, which began anteriorly at the umbilicus and xiphoid process respectively, fused posteriorly to form a single patch at the level of the costal margin. The highest band extended across the pectoral region and in the areola formed papillary growths.

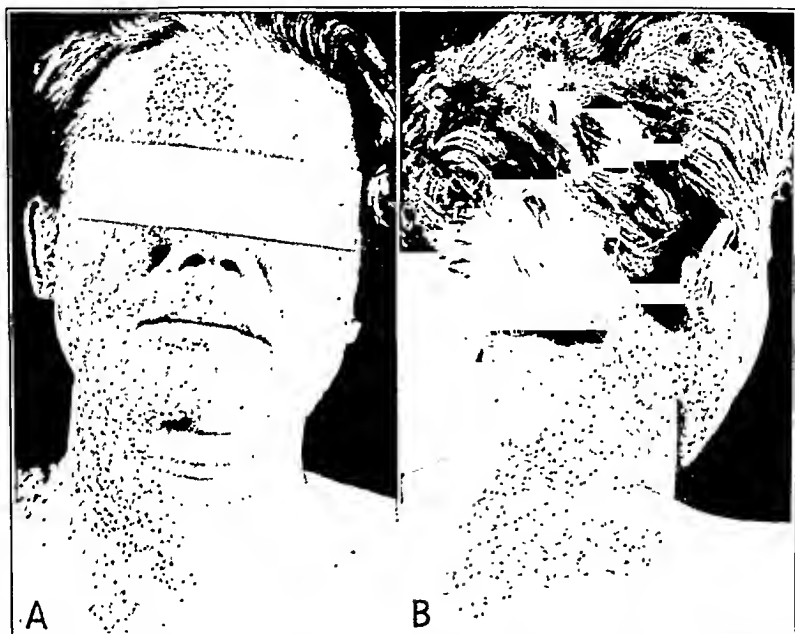


Fig. 14 (case 5).—Lentiginous nevus. *A*, anterior view showing sharp limitation of the nevus at the median line. *B*, right posterolateral view. Note the involvement of the neck and upper part of the back.

It extended into the axilla and ended in the scapular region posteriorly. From this band isolated streaks extended onto the arm both anteriorly and posteriorly. On the posterior aspect of the shoulder were several scattered small groups, and near the median line of the back were several more isolated patches and lines, which extended down to the midlumbar region.

There was a transverse band of papillary lesions across the entire anterior aspect of the neck and the submental region. Posteriorly, however, the cervical lesions were confined to the left side, with one thick streak running down the median line to the level of the last cervical vertebra. In the left temporo-frontal region was another scattered group of nevi.

OTHER NEVI OF UNILATERAL DISTRIBUTION

Two other conditions which are unilateral nevi but of the lentiginous type and therefore not considered suitable for this series are shown in figures 14 and 15. They had both been present since birth and had caused no symptoms. Biopsy of the nevus in another case (fig. 16) showed accumulations of pigment in the cells of the basal epithelial layer and some perivascular round cell infiltration of the corium.

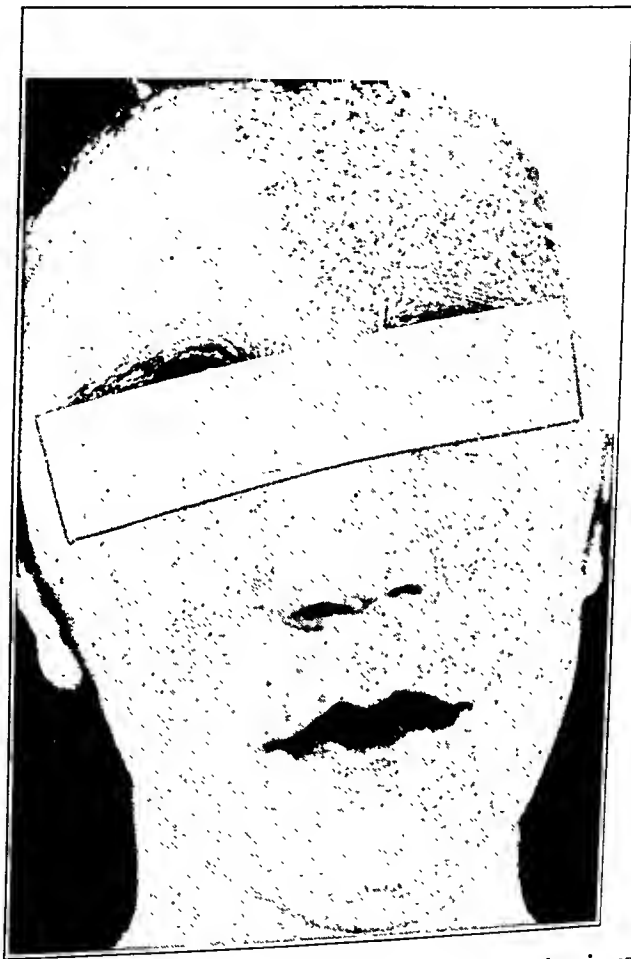


Fig. 15 (case 6).—Lentiginous nevus, less pronounced than that in case 5 but also sharply demarcated at the median line.

ANALYSIS OF CHARACTERISTICS OF NAEVUS UNIS LATERIS

The cases of naevus unis lateris which have been reported in the literature, together with our own cases, have been reviewed with the purpose of determining the various characteristics of this unusual tumor. The criteria for determining the suitability of the cases have been: (1) verrucous or papillary nevi; (2) linear configuration of the lesions; (3) predominantly unilateral distribution, and (4) involvement of sufficient extent to make the peculiarity of essentially unilateral distribution self evident.

There were 156 cases in which the lesions fulfilled these criteria. These, with the addition of our own 4 cases, made a total of 160. In an analysis of the nevi the following factors have been taken into consideration: (1) race; (2) sex; (3) distribution or location of the nevus; (4) age incidence; (5) heredity; (6) pigmentation; (7) relation to nerve distribution; (8) histopathologic appearance; (9) symptoms; (10) treatment; (11) course of the disease, and (12) presence of other congenital abnormalities or other unusual features.



Fig. 16.—Photomicrograph of a section of nevus removed from the base of the neck. Increased pigment in the cells of the basal epithelial layer can be seen.

Race.—Hasselmann's patient²⁷ was a Filipino, and the author stated the belief that the nevus was the only one reported as occurring in a person of this race. It was an extensive pigmented nevus appearing at birth and involving the right side of the trunk, right thigh, leg and foot. The patient was a 13 year old boy. One Negro appeared in the series, his case being reported by Paromaganian.²⁸ This patient had a verrucous lesion on the right side, involving the neck, axilla, shoulder, trunk, thigh, foot and leg. The age at which it appeared was not known. At the time

²⁷ Hasselmann, *Journal of the American Medical Association*, 1941, Vol. 117, No. 1, p. 10.

²⁸ *Id.*, 1941, Vol. 117, No. 1, p. 10.

A provisional diagnosis can be verified by roentgen examination of the chest; lateral films are particularly valuable in demonstrating the mediastinal air. If the emphysema is extreme, pneumoperitoneum may be demonstrated by a roentgenogram of the abdominal cavity.

SUMMARY

A case of mediastinal emphysema with bilateral pneumothorax, with death following radical dissection of the neck is reported. The cause, mechanism, treatment and prevention of the condition are discussed.

STORED DEXTROSE-CITRATE PLASMA IN THE TREATMENT OF OPERATIVE SHOCK

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IOWA CITY

There have been several reports dealing with the value of plasma in the treatment of shock.¹ This has been the result of the establishment and general acceptance of certain tenets concerning plasma: (1) transfusions of plasma may be given without regard to blood groups; (2) plasma may be obtained from stored whole blood that is too old to use as it is; (3) plasma may be stored for long periods and remain efficacious. The purpose of this paper is to report certain experiences acquired by using plasma in the treatment of shock associated with operative procedures in the surgical service of the University Hospitals.

TYPE OF SHOCK ASSOCIATED WITH OPERATIONS

The problem of defining clinical shock offers considerable difficulty. Certain authors have separated shock and hemorrhage and have described distinguishing features for each. It remains, however, the general practice to designate as shock conditions in which there is an acute lowering of blood pressure. I have found it practical to consider "shock associated with operations" as a broad term describing a state of circulatory

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This study was made in cooperation with Dr. Elmer J. DeGowin, Department of Medicine.

1. (a) Elliott, J.; Busby, G. F., and Tatum, W. L.: Preparation and Preservation of Dilute Plasma, *J. A. M. A.* **115**:1006 (Sept. 21) 1940. (b) Strumia, M. M.; Wagner, J. A., and Monaghan, J. F.: Use of Citrated Plasma in Treatment of Secondary Shock, *ibid.* **114**:1337 (April 6) 1940. (c) Levinson, S. O.; Neuwelt, F., and Neeheles, H.: Human Serum as a Blood Substitute in the Treatment of Hemorrhage and Shock, *ibid.* **114**:455 (Feb. 10) 1940. (d) Tatum, W. L.; Elliott, J., and Nessel, N. M.: A Technique for the Preparation of a Substitute for Whole Blood Adaptable for Use During War Conditions, *Mil. Surgeon* **85**:481 (Dec.) 1939. (e) Lehman, E. P.: A Simple Method of Plasma Transfusion, *Correspondence*, *J. A. M. A.* **112**:1406 (April 8) 1939. (f) Mahony, E. B.: Study of Experimental and Clinical Shock with Special Reference to Its Treatment by Intravenous Injections of Preserved Plasma, *Ann. Surg.* **108**:178 (Aug.) 1938. (g) Bond, D. D., and Wright, D. G.: The Treatment of Hemorrhage and Traumatic Shock by the Intravenous Use of Lyophilic Serum, *ibid.* **107**:500 (April) 1938.

insufficiency in which there is a fall of the systolic blood pressure below 80 mm. of mercury. The circulation does not function efficiently when the arterial tension is lower than this value. One may then recognize several types of shock. Primary or neurogenic shock is essentially a vasomotor phenomenon, characterized by arteriolar relaxation without hemoconcentration; usually in this type the pulse rate is not increased. Spinal anesthesia frequently causes this syndrome, which, if not relieved, may develop into secondary shock. Secondary shock, often called surgical or traumatic shock, is characterized by capillary dilatation, atonicity and increasing permeability; this type results in hemoconcentration. According to Moon,² this is the only condition that should be considered as true shock. Shock secondary to hemorrhage is brought about by the decrease in circulating blood volume caused by loss of both plasma and red cells. At first there is a tendency toward hemoconcentration of the remaining blood; later, hemodilution occurs.

One feature of shock, regardless of type or causative factors, is reduced circulating blood volume. In severe shock crystalloid solutions injected intravenously pass quickly out of the vascular system into the tissues and produce only a transient increase in circulating blood volume. Plasma, serum and lyophil serum, however, are retained in the vascular system and contribute a more permanent increase in circulating blood volume.^{1c, f, g}

GENERAL CONSIDERATIONS CONCERNING THE USE OF DEXTROSE-CITRATE PLASMA

In the blood bank of the University Hospitals, blood is stored in the Rous-Turner dextrose-citrate mixture, as modified by DeGowin, Harris and Plass.³ This mixture consists of 10 volumes of blood, 13 volumes of 5.4 per cent dextrose in water and 2 volumes of 3.2 per cent sodium citrate (dihydric) in water. Blood is stored in this mixture at 2 C. for thirty days before it is considered unfit for transfusions. At the expiration of the limit of storage, the supernatant dextrose-citrate plasma is pipetted off from the sedimented erythrocytes and the latter discarded. Thereafter the dilute plasma is kept refrigerated and employed in the treatment of operative shock. No antiseptics are added to the plasma mixture. The concentration of free hemoglobin in the dilute plasma is always less than 25 mg. per hundred cubic centimeters. Transfusions of the plasma mixture are given without

2. Moon, V.: *Shock and Related Capillary Phenomena*, New York, Oxford University Press, 1938.

3. DeGowin, E. L.; Harris, J. E., and Plass, E. D.: *Studies on Preserved Human Blood: I. Various Factors Influencing Hemolysis*, J. A. M. A. **114**:850 (March 9) 1940.

regard to the isoagglutinins. Eighty-nine plasma transfusions have been given; of which twenty-six were employed in the treatment of shock. No transfusion of the latter series was accompanied by chills or fever. The only febrile reaction encountered in the entire series occurred in a patient receiving his sixth plasma transfusion for the supplement of plasma proteins.

Since hemorrhage, neurogenic reflexes and tissue trauma all play a part in causing the shock that is seen in patients during or following operations, it is sometimes difficult to assign the condition to any one of the aforementioned three categories. With current anesthetic methods and preoperative preparation, severe shock associated with general surgical operations is infrequent. During the year 1939 there were 1,892 major operations performed by the general surgical staff at the University Hospitals. There were 68 instances of secondary shock or shock secondary to hemorrhage during or after the operations. There were 50 cases of primary shock, in all of which this condition was alleviated without intravenous injection of fluid. In several cases in this series the condition could be classified as mild shock.

EFFICACY OF PLASMA IN THE TREATMENT OF SHOCK

Dextrose-citrate plasma was given to 26 patients who manifested shock during or after operations. Data on 18 of these patients are given in the table. Hematocrit determinations were made before operation, at the beginning of plasma transfusion, on the day following operation and on subsequent days. In every case a satisfactory recovery from a state of shock ensued. The amount of blood lost during operation was determined by dissolving the hemoglobin from the sponges and drapes in water, and determinations of hemoglobin were made by using the Kletts-Summerson photocolormeter. The patient's hemoglobin had been determined before operation, and by proportion to the amount of hemoglobin lost, the volume of blood lost was computed.

There is one question concerning the use of plasma which immediately presents itself: Is plasma alone adequate in the treatment of shock associated with severe hemorrhage? In most of the cases the loss of blood was moderate, but in 2 it was excessive. In case 1, the blood loss was 320 cc., which represented 23 per cent of the patient's estimated total blood volume. The hematocrit determination was 32 at the time plasma transfusion was started, and the child was then in severe shock. Shock was alleviated within thirty minutes, but eighteen hours later the hematocrit determination was 23, indicating marked anemia. One may state that dextrose-citrate plasma was highly satisfactory in alleviating shock in these cases, even when the

The Effect of Dextrose-Citrate Plasma Transfusion in Operative Shock

Patient, Sex and Age (Yr.)	Type and Time of Operation	Blood Loss (Per Cent of Total Volume and Cc.)	Clinical Condition When Treatment Was Begun	Quantity of Dextrose- Citrate Plasma Given (Cc.)	Result	Before Operation	During Shock	Hematocrit Determinations									
								Days After Operation									
								2	3	4	5	6	7	8	9	10	
1 F 7	Sequestrectomy (45 min.)	23% (310 cc.)	B.P. 0/0; pulse weak; pulse rate 160; extremities cold	650	Response in 10 min.; recovery complete within 25 min.	..	32	23	22†	30	31
2 F 45	Repair of ventral hernia (3 hr.)	16% (960 cc.)	B.P. 78/60; pulse weak; pulse rate 123; perspiring; extremities warm	650	Recovery complete within 20 min.	45	45	33	31	31	34
3 M 43	Thoracoplasty, first stage (2½ hr.)	16% (920 cc.)	B.P. 60/40; pulse weak; pulse rate 120; perspiring	1,400	Recovery complete within 20 min.	52	44	38	36	..	37
4 F 44	Radical mastectomy (2¼ hr.)	14.5% (700 cc.)	B.P. 60/40; pulse weak; pulse rate 90; perspiring; extremities cold	650	Recovery complete within 30 min.	49	48	32	..	34	..	34	..	35
5 M 50	Abdominoperineal resection of the rectum (2 hr.)	10% (612 cc.)	(During operation) B.P. 20/0; pulse imperceptible; extremities cold and clammy	1,800	Response in 15 min.; B.P. 90/60 at end of operation; 30 minutes later, 120/80	41	39	32	..	28	..	33†	..	36
6 F 43	Radical mastectomy (2 hr.)	9.5% (412 cc.)	B.P. 50/0; pulse weak; pulse rate 110; perspiring; extremities warm	650	Recovery complete within 30 min.	42	38	30	..	29	..	29	..	30
7 M 39	Thoracoplasty, second stage (1¼ hr.)	9.5% (500 cc.)	B.P. 70/50; pulse weak; pulse rate 120; perspiring; extremities warm	650	Recovery complete within 30 min.	47	46	38	..	35	..	36
8 M 34	Thoracoplasty, first stage (2 hr.)	9% (470 cc.)	B.P. 60/0; pulse weak; pulse rate 130; perspiring; extremities cool	700*	Recovery complete within 20 min.; given later transfusion	52	48	39	41

9 F	Thoracoplasty, second stage (1½ hr.)	9% (420 cc.)	B.P. 80/60; pulse weak; pulse rate 140; perspiring; extremities cool	700*	Recovery complete within 30 min.	41	42	34	33	31
36 F	Radical mastectomy (3 hr.)	8% (500 cc.)	B.P. 80/60; pulse weak; pulse rate 130; perspiring; extremities warm	1,100	Recovery complete within 20 min.	40	38	30	28	30	..	32	..
10 F	Revision thoreo- plasty (2 hr.)	7.5% (392 cc.)	B.P. 78/53; pulse weak; pulse rate 124; perspiring; extremities warm	650*	Recovery complete within 20 min.	40	39	26	27	28
41 F	Thoracoplasty, second stage (2 hr.)	7.5% (470 cc.)	B.P. 60/0; pulse weak; pulse rate 160; perspiring; cold, clammy, cyanotic	600	Recovery complete within 20 min.	40	40	37	36	36
12 M	Vaginal hysterec- tomy (1½ hr.)	Large	B.P. 70/40; pulse weak; pulse rate 140; perspiring; cold and clammy	625	Recovery complete within 30 min.	..	40	25	24	23	..	28	..
40 F	Nephrectomy (2 hr.)	Large	B.P. 72/33; pulse weak; pulse rate 130; perspiring; extremities warm	650	Recovery complete within 30 min.	..	31	29	21	22
42 F	Abdominoperineal resection of rectum (2 hr.)	7% (300 cc.)	B.P. 60/40; pulse weak; pulse rate 100; perspiring; extremities cold	1,200	Recovery complete within 20 min.	51	55	35	34	36	..	38	..
16 M	Exploratory laparotomy and appendectomy (1 hr.)	Small	B.P. 80/60; pulse weak; pulse rate 70; extremities warm (primary shock)	650	Recovery complete within 15 min.	..	48	47
28 M	Gastroenterostomy (1½ hr.)	Small	B.P. 80/60; pulse weak; pulse rate 80; warm (largely primary shock)	650	Recovery complete within 15 min.	37	36	38	42	42
17 F	Resection of ileum; anastomosis (ease of intestinal obstruc- tion) (3½ hr.)	Small	B.P. 70/60; pulse weak; pulse rate 120; perspiring; extremities warm	1,200	Recovery slow; B.P. 120/80 after 1 hr.; died on 3d postopera- tive day of peritonitis	52	55	44

* These patients received dextrose-urate plasma from Baxter flasks. Merthiolate was added as an antiseptic, and the flasks were stored at room temperature for periods of twelve, fourteen and sixteen weeks.

† Indicates transfusion of whole blood.

loss of blood had been relatively large. Considerable experimental evidence has been accumulated to show that a large percentage of red cells may be lost and yet adequate compensation will follow, provided that plasma is restored and oligemia thus prevented.^{1c} Since both whole blood and plasma were available, it was thought inadvisable to use plasma and withhold whole blood in cases of severe hemorrhage merely to learn just how much loss of red cells the human organism is capable of withstanding, provided the volume is made up by plasma. Thus in craniotomies, in which the blood loss is often over 1,000 cc., preserved dextrose-citrate whole blood is used routinely.

There are some instances in which the use of plasma is preferable to that of whole blood. This is illustrated in the case of patient 18. She had an intestinal obstruction of four days' duration. At operation the obstruction was found to be due to adhesions, and resection of a loop of the ileum was necessary. The patient was markedly dehydrated on admission, and in spite of intravenous injection of fluids, the hematocrit determination was 52 when the operation was begun. Signs of shock were manifest after an hour, and at this time the hematocrit determination was 55. Thus there was considerable hemoconcentration, the viscosity of the blood was increased, and plasma was preferable to whole blood transfusion. Operations on the gastrointestinal tract usually cause hemoconcentration if they are not associated with considerable blood losses. When these patients have a high hematocrit determination before operation, the use of plasma is preferable to that of whole blood if shock is manifest. In any instance in which it is desirable to increase the circulating blood volume and red cells are not urgently needed, it may be argued that transfusions of plasma are preferable to those of whole blood since they do not carry the danger of hemolytic reactions.

Kekwick and co-workers⁴ recently reported their experiences in the treatment of shock associated with air raid casualties. Multiple contusions, lacerations and compound fractures were frequent. The patients were usually seen one to three hours after injury and were in severe shock. Plasma was found effective in raising blood pressure, but it was often necessary to give 2,000 to 3,000 cc. to alleviate shock. The losses of circulating blood were often estimated to exceed 2,000 cc. In general, the hemoglobin determinations and hematocrit readings were normal on admission, but after recovery from shock, values were usually at least 50 per cent below normal. Thus there was a significant decrease in circulating red cells, and these workers formed the opinion that "when the amount of transfused fluid needed reaches three 540 cc.

4. Kekwick, A.; Maycock, W. d'A.; Marriott, H. L., and Whitby, L. E. H.: Diagnosis and Treatment of Secondary Shock, *Lancet* 1:99 (Jan. 25) 1941.

bottles or more, at least one bottle in three should be blood." It is my opinion that plasma is efficacious in relieving operative shock when treatment is instituted immediately, even though there is associated a relatively large loss of blood. It should be noted, however, that the types of shock in my cases and in those of other American authors ^{1b} certainly are not comparable to the severe type of shock of several hours' duration that Kekwick and his associates have been called on to treat, and their conclusions regarding the desirability of whole blood appear logical.

SUMMARY

Stored dextrose-citrate plasma was efficacious in treating a series of patients manifesting shock associated with general surgical operations.

Plasma for this purpose may be obtained by aspiration of the supernatant fluid from blood stored for thirty days in dextrose-citrate preservative.

It is pointed out that treatment of shock in our cases was started immediately on development, and therefore our cases are not comparable to the cases of severe shock seen as a consequence of war injuries.

FOREIGN BODIES IN THE BILIARY TRACT

REPORT OF A CASE WITH A TABULAR REVIEW OF THE LITERATURE

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Foreign bodies in the biliary tract are of sufficient rarity to make the report of this case—in which a rubber catheter was present in the common duct—of interest. The fact that the lumen of a rubber tube may be obliterated by the deposition of bile salts is a serious objection to the use of rubber tubing in operations for the reconstruction of the biliary passages.

REPORT OF CASE

The patient, a 37 year old white woman, was admitted to the West Baltimore General Hospital April 10, 1935. She showed symptoms and signs suggestive of appendicitis, and a McBurney appendectomy was done. The gallbladder was said to be normal to palpation. The patient's postoperative course was uneventful, and she was discharged nine days after admission.

The patient was readmitted four months later with typical signs and symptoms of acute cholecystitis. At operation a gallbladder containing two stones was removed, and the hepatic and common ducts were observed to contain many stones. The common duct was opened, and the stones were evacuated. A Dakin tube was inserted through the stump of the cystic duct, and a size 20 F catheter was inserted into the common duct. Both of these tubes were sutured to the respective ducts with plain size 0 gut. The temperature was moderately elevated for several days following the operation. On the fourth day after operation an attempt was made to remove the catheter, but the distal $1\frac{1}{2}$ inches (3.8 cm.) of the tube was accidentally broken off and left in the abdomen. The Dakin tube, however, was successfully removed. The further postoperative course was uneventful, and on the thirteenth day after operation a roentgenogram of the abdomen showed the distal portion of the tube to be in the right upper quadrant. On the eighteenth day the patient was discharged.

The patient had no further difficulty until about four years later, when she began to have attacks of pain in the right upper quadrant radiating to the subscapular region and nausea, vomiting, belching and, occasionally, jaundice. These attacks were infrequent at first but later became closer together and more severe.

On physical examination the patient was noted to be an apprehensive, well developed and well nourished woman of some 40 years, who was lying in bed with no apparent pain. The temperature and the pulse rate were within normal

From the surgical service of Dr. E. S. Johnson at the West Baltimore General Hospital.

Foreign Bodies in the Biliary Tracts

Author and Date	Age of Patient	Symptom-Interval	Symptoms	Nature of Foreign Body	Site of Foreign Body	Manner of Reaching Bile Duct	Length of Time in Bile Duct	Calcareous Deposits	Result
Oppel: Zentralbl. f. Chir. 53: 889, 1926	?	? ? ?	?	Swab	Common duct	Probably migrated from peritoneum	4 mo. ?	?	Death from peritonitis
Lemierre and Pollet: Bull. et mem. Soc. med. d. hop. de Paris 51: 311, 1927	40	?	"Stitch" in lower part of thorax; dry cough without expectoration; emaciation	Handle of spoon 13.5 cm. long	Handle was in common duct and extended to liver	Ingested by insane patient	?	Spoon handle markedly oxidized	Death
Fedoroff: Zentralbl. f. Chir. 57: 637, 1930	39	2½ yr.	Attacks of colic; occasional jaundice	Horizontal part of T tube 6 cm. long	Retroduodenal part of common duct	Broke off nt operation on attempted removal	4½ yr.	Covered with "Gallensand"	Recovery
Goldman: Zentralbl. f. Chir. 57: 2631, 1930	36	14 yr.	Severe pain	Copper bullet	Cystic duct	Bullet wound	15 yr.	The bullet was covered with a gritty brownish precipitate	Recovery
Eichelner: Zentralbl. f. Chir. 58: 671, 1931	39	16 mo.	Pain in right upper quadrant of abdomen with jaundice	Cotton fibers	Common duct	From drainage operation	17 mo.	The cotton fibers were encrusted	Recovery
Cook: Brit. M. J. 1: 810, 1932	65	?	Indigestion; nausea; pain in right upper quadrant of abdomen	Piece of L-shaped wire less than 1 inch (2.5 cm.) long and 0.001 inch (0.0025 cm.) thick	Common duct	Probably ingested	?	None	Recovery
Voland: Ann. Surg. 98: 901, 1933	49	Approximately 4 mo.	Jaundice and anemia	Cotton gauze 1 by 1 by 5 cm.	Common duct	Operation	6 mo.	The gauze was impregnated with bile salts and fibrin	Death
Crawford and Stewart: Am. J. Clin. Path. 9: 353, 1933	53	3 wk.	Painless jaundice with clay-colored stools and hemorrhage	Hemostatic blade 4.2 cm. long	Hepatic duct	Operation	7 yr.	The blade was covered with dark green friable pigment coagulation	Death
Bowen: Arch. Surg. 43: 168, 1911	42	1 yr.	Biliary colic jaundice	Size 20 F catheter 2 inches (3.5 cm.) long	Common duct	Operation	5 yr.	Tube was covered with and occluded by greenish calcareous deposits	Recovery

limits. The thyroid gland was firm to palpation and symmetrically and diffusely enlarged. No bruit was heard. The blood pressure was 140 systolic and 80 diastolic. Well healed right upper rectus and McBurney incisions were present. Some tenderness was noted in the epigastrium and in the right upper quadrant, and there was slight rigidity of the right upper rectus muscle.

The Eagle test of the blood was negative; the hemoglobin value was 84 per cent (Sahli) and the leukocyte count was 10,000, with 82 per cent polymorphonuclear neutrophils. The icteric index was 7.6. On roentgenologic examination a drainage tube was noted in the right upper quadrant of the abdomen and a stone was seen in the pelvis of the left kidney. Gastrointestinal fluoroscopy showed distortion of the second portion of the duodenum suggestive of adhesions in the right upper quadrant of the abdomen. The basal metabolic rate was $+0.6$ per cent.

The patient was taken to the operating room; while she was under nitrogen monoxide-ether anesthesia, a right upper paramedian incision was made. The rubber tube was easily felt, and it was grasped through the wall of the common duct with Allis forceps. Then a small longitudinal incision was made in the common duct, and through this the tube fragment was removed. The common duct was about $\frac{1}{2}$ inch (1.27 cm.) in diameter and contained greenish flaky calcareous debris. A size 10 F ureteral catheter was inserted into the common duct and through the ampulla of Vater into the duodenum. About 20 cc. of solution of sodium chloride was injected, and, as none of this fluid regurgitated, it was assumed that the tip of the catheter was in the duodenum. The common duct was irrigated with solution of sodium chloride until no more calcareous material could be evacuated. A new size 12 F rubber catheter was inserted into the common duct with the eye end pointing toward the liver. The tube was sutured to the common duct with plain size 0 gut, and the tube, together with a cigaret drain placed to the site of the opening in the common duct, was brought out through a stab wound in the right flank.

Examination showed the removed piece of tubing to be the end of a size 20 F. catheter about 2 inches (5 cm.) long. The tip had been cut off before the catheter was inserted. The lumen of the tube was completely occluded at both ends by dark greenish calcareous deposits, and the surface of the tube was covered with this material. When the tube was bent, this calcareous material scaled off the surface of the tube in flakes, and on further bending the tube was broken. It was thought that the rubber tube may have acted as a ball valve in the common duct, causing intermittent obstruction.

The postoperative course was marked by elevation of temperature which reached 101 F. every day until the sixth day, when it gradually began to descend to normal. The common duct catheter and the cigaret drain were removed on the fifth and the sutures on the sixth day after operation. Following this, some bile drained, but the drainage gradually diminished, and a few days before the patient was discharged on the twentieth postoperative day, drainage had stopped entirely.

COMMENT

A foreign body may enter the biliary passages (1) from the gastrointestinal tract through the ampulla of Vater, (2) at the time of an

operation on the biliary tract or (3) through a nonoperative wound. The objects found include swabs, thread, bristle, gauze, fruit seeds, steel needles, pieces of wire, a spoon handle, bullets, rubber drains and absorbable and nonabsorbable suture materials. Various parasites, not properly being foreign bodies, are not considered here. In order to avoid leaving portions of rubber drains in the biliary tract, the use of well made new tubing should be insisted on. The tubing used should be such as can be visualized roentgenographically. The table summarizes the pertinent facts concerning cases reported in the literature.

VENOUS THROMBOSIS

EARLY DIAGNOSIS WITH THE AID OF PHLEBOGRAPHY AND ABORTIVE
TREATMENT WITH HEPARIN

GUNNAR BAUER, M.D.

MARIESTAD, SWEDEN

Since Jorpes¹ by his work at Karolinska Institutet in Stockholm in 1935 defined the chemical nature of heparin and made this physiologic anticoagulant of Howell available in a pure form, he and his co-workers, as well as other Swedish investigators, have been trying to determine the clinical serviceability of this preparation. Their efforts have been successful. Their results and those of the group in Toronto, Canada, working on the same problem have been summarized in two monographs, by Jorpes² and Mason.³

One of the most important questions was whether heparin could be used in treating thromboembolic disease. Some valuable work on this problem has been done independently by Crafoord⁴ and Crafoord and Jorpes⁵ in Stockholm and by Murray and Best in Toronto. In several studies, based on 500 cases, Crafoord has shown that in no instance has postoperative thrombosis appeared in patients who have been subjected to regular treatment with heparin. Such treatment, however, must begin a few hours after operation and continue without a break for five to ten days or longer, with four intravenous injections daily.

Crafoord's studies have shown that in heparin there is available an almost infallible prophylactic against thromboembolism. But valuable though heparin is, practical reasons unfortunately preclude its more general use for prophylaxis. If all patients operated on were treated with heparin, the cost would be prohibitive and the demands on the staff too heavy.

From the General Hospital, Gunnar Bauer, M.D., Head Surgeon.

Read at the joint meeting of the Swedish Association of Surgeons and the Swedish Association of Internal Medicine, Stockholm, Dec. 1, 1940.

1. Jorpes, J. E.: *Naturwissenschaften* 23:196, 1935; *Biochem. J.* 29:1817, 1935.
2. Jorpes, J. E.: *Heparin: Its Chemistry, Physiology and Application in Medicine*, New York, Oxford University Press, 1939.
3. Mason, M. F.: *Surgery* 5:451 and 618, 1939.
4. Crafoord, C.: *Acta chir. Scandinav.* 79:407, 1937; 82:319, 1939.
5. Crafoord, C., and Jorpes, E.: *Heparin as a Prophylactic Against Thromboses*, J. A. M. A. 116:2831 (June 28) 1941.

Nonetheless, heparin seems to be too good and too innocuous an anticoagulant to be abandoned. Perhaps its use might suitably be restricted to the treatment of patients who already have thromboembolism. In such practice, however, another difficulty would be immediately evident, for the experience of Crafoord and others has shown that patients with fully manifest thrombosis are not greatly benefited by treatment with heparin.

The idea then suggested itself that the treatment of thrombosis should begin at a much earlier stage, that is, immediately after the very first manifestations of the disease had appeared. In other words, the treatment should be given not to patients who have thrombosis but to those who are just getting it. Unfortunately, the early and transitory stage of thrombosis evades recognition by ordinary clinical methods. However, by means of phlebography thrombotic conditions in an early stage, *in statu nascendi* it might be said, may be revealed.

In this paper a short description of this method will be given and the question of its significance for heparin treatment will be considered.

METHOD OF PHEBOGRAPHIC EXAMINATION

Phlebography, in the sense the term is used here, refers to a method, available for the past two years, which makes it possible to render visible on the x-ray film the deep venous trunks of both the leg and the thigh.

The method used is based on one originated by dos Santos,⁶ which has been considerably modified and standardized at the General Hospital of Mariestad. The technic has been fully described in earlier works.⁷ It will suffice to state here that with the patient lying on his back a small incision, about 1 cm. in length, is made behind the outer malleolus, and a superficial, rather thick, subcutaneous vein, which is a tributary of the small saphenous vein, is exposed. Into the exposed vein is slowly injected 20 cc. of a 35 per cent solution of perabrodil (diodrast). After about sixty seconds the x-ray film placed under the patient's leg is exposed. The injected vein has numerous anastomoses with the deep veins of the lower part of the leg, and in the roentgenograms of normal patients these veins will therefore show up well filled with the opaque medium. On the other hand, should the deep veins be clogged with thrombotic masses, considerable filling defects or absence of the contrast shadows will be evident on the roentgenogram. Four characteristic phlebograms are reproduced in figure 1.

ORIGIN AND COURSE OF THROMBOSIS

I have made about one hundred and fifty phlebographic examinations, and in my opinion, use of this method casts new light on many phases of the problem of thromboembolism and gives rise to a number of speculations. Most of these I discussed at length in a previous publica-

6. dos Santos, J. C.: *J. internat. de chir.* 3:625, 1938.

7. Bauer, G.: (a) *Nord. med.* 8:1788, 1940; (b) *Acta chir. Scandinav.* (supp. 61) 84:1, 1940.

tion.^{7b} Only two aspects, of special importance for diagnosis and therapy, will be dealt with here.

One result of phlebographic studies is the revised, and probably more correct, view of the origin and inherent nature of thromboembolic disease to which it has given rise. By the term thromboembolic disease is meant, of course, a condition of progressive, or creeping, thrombosis. It thus implies that the thrombotic mass is located in a vein of considerable caliber, that is, a collecting trunk of lower or higher order, and that this thrombotic mass is undergoing continual accretion by the deposition on it of fresh quantities of blood corpuscles and fibrin.

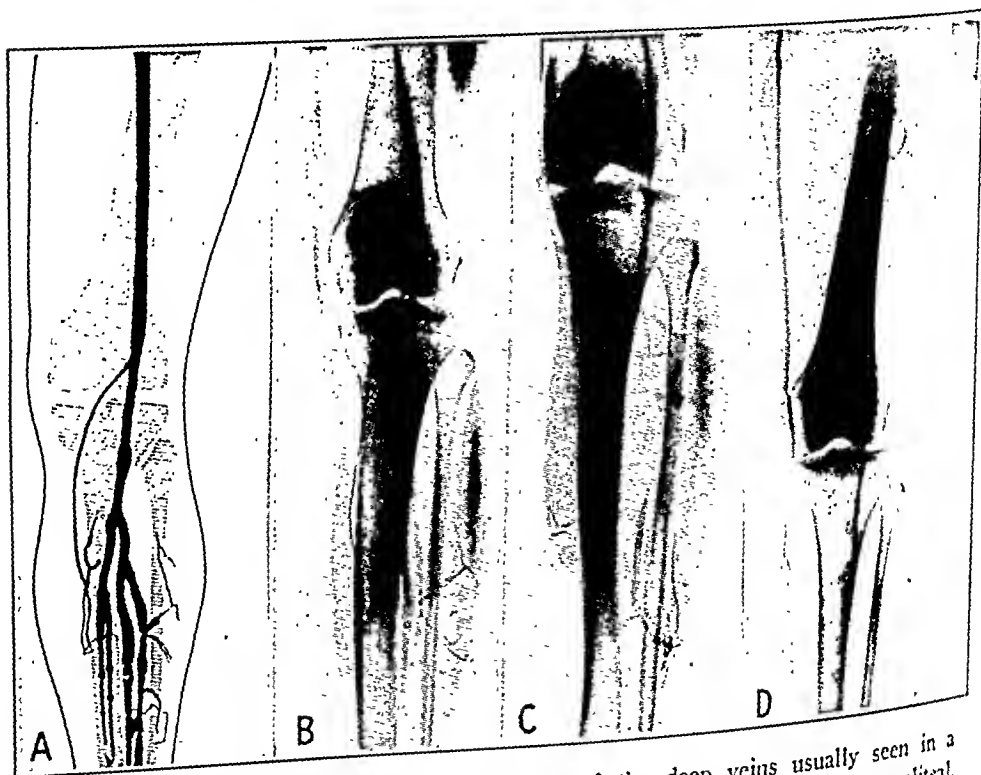


Fig. 1.—*A*, diagrammatic representation of the deep veins usually seen in a normal phlebogram. There is good contrast filling of the femoral, the popliteal, the anterior tibial (in the space between the tibia and the fibula) and the posterior tibial veins. Only a few subcutaneous veins are visible. *B*, normal phlebogram. *C*, recent thrombosis localized to the lower part of the leg. There is no contrast filling of the posterior tibial or of the upper part of the anterior tibial veins. *D*, recent thrombosis of the leg and thigh (phlegmasia alba dolens). There is no contrast filling either of the large, deep venous trunks of the lower part of the leg or of the popliteal or the femoral veins. Only the large saphenous vein and a few superficial veins are visible.

For a long time it was generally thought that the process giving rise to large thrombi started in the large pelvic veins or in the upper portion of the femoral vein. During the last decade, however, this view has been undermined. The work of clinicians and pathologists, and of

whom may be mentioned Homans,⁸ Rössle,⁹ Neumann¹⁰ and Frykholm,¹¹ has shown that the starting point of the process, at any rate in a large percentage of cases, must be in the veins of the lower part of the leg. Phlebography has made a more thorough study of this question possible. I believe that one is now justified in making the statement that almost without exception the thrombotic process has its origin in the deep venous trunks of the lower part of the leg.

By using the phlebographic method and by constantly comparing the roentgenograms with the clinical findings, I have come to the conclusion that the origin and course of thromboembolic disease may be reconstructed as follows:

The whole process starts with a clot, which arises for some unknown reason, protruding from a muscle vein into the lumen of one of the thick venous trunks of the lower part of the leg. It becomes the starting point of a deposition thrombus, which subsequently goes on growing in the direction of the blood stream. Even this first stage can be phlebographically demonstrated, though it will doubtless evade recognition by other methods. In the next stage the large veins of the lower part of the leg are progressively filled, the thrombotic masses in course of time completely filling the lumens and becoming firmly attached to the walls of the vessels. Concurrently, there proceeds a longitudinal growth up through the femoral vein. As a result this vein will eventually contain, freely waving about in the blood stream, an eel-like formation, 40 to 50 cm. long, dark red and with a smooth, slippery surface. This thrombotic structure forms, as it were, a cast of the great vein's lumen, though it does not completely occlude the latter. The wall of the vein is as yet not involved in any way, and the thrombus is anchored only at its lower end, far down in the lower part of the leg.

This condition, which obviously entails great risk of embolism, appears to be commoner than was formerly supposed and, strangely enough, cannot be diagnosed by ordinary clinical methods. The phlebographic examination, however, is a means of unmasking the situation.

In its further development the condition may now follow different lines. The waving thrombus may give rise to an embolus by breaking off at some point and floating up toward the heart. The commonest course, however, is for the thrombus to continue to increase in thickness, so that it entirely blocks the lumen, begins to involve the endothelium of the wall of the vein and becomes firmly fixed to the wall along its

8. Homans, J.: *J. internat. de chir.* **3**:599, 1938.

9. Rössle, R.: *Virchows Arch. f. path. Anat.* **300**:180, 1937.

10. Neumann, R.: *Virchows Arch. f. path. Anat.* **301**:708, 1938.

11. Frykholm, R.: *Surg., Gynec. & Obst.* **71**:307, 1940.

entire length. The typical picture of phlegmasia alba dolens arises, followed later by one of the several clinical pictures of chronic thrombosis.

In many cases the thrombotic process extends farther and invades the pelvic veins. This occurrence is not associated with clinical symptoms of any considerable prominence, unless there is too great extension, when death may ensue from closure of veins vital to life, for example the renal or mesenteric veins.

Not infrequently the process becomes bilateral. Phlebographic examination shows, however, that in such cases, too, the thrombosis on the other side of the body probably always starts in the lower part of the leg.

DIAGNOSIS OF THROMBOSIS BY PHLEBOGRAPHIC EXAMINATION

This short exposition should make it easier to realize that a surer and earlier diagnosis of thrombosis can be made by phlebographic examination than by the methods hitherto used. It is obviously unnecessary to enumerate here all those elements in the clinical examination which are designed to unmask an early stage of thrombosis. A common feature of them all is that they are unsatisfactory in two types of cases. In the one type the clinical signs are pronounced and incontestible. Phlebographic examination teaches, however, that in cases of this nature the thrombosis is neither recent nor confined to the lower part of the leg. On the contrary, tenderness and swelling do not appear until the thrombotic masses have become firmly attached to the walls of the veins of the lower part of the leg and have produced irritation of the walls, with periphlebitis. And at this stage, of course, there is often present in the femoral vein a large, waving, potentially dangerous thrombus.

In the other type of case the clinical signs of thrombosis are extremely vague and scarcely more than suggestive. In cases of this kind an early stage of thrombosis may be present, but it would be incorrect and misleading to make a diagnosis of thrombosis solely on the basis of such signs. In at least 15 cases of this type I have been able roentgenographically to exclude the presence of thrombosis. In none of these cases did thrombosis subsequently appear.

To insure an early, and at the same time reliable, diagnosis by means of the phlebographic examination, however, one must obviously be exceedingly watchful. Naturally, the examination must not be put off until cleancut clinical symptoms have developed. Moreover, a large number of patients who may be threatened with the thrombosis cannot be phlebographically examined at random. The right procedure must be to keep such patients at all the times under the strictest supervision. Heed must be given to the slightest unexplained rise in the pulse rate.

or the temperature, to any unmotivated general restlessness, to the least signs of pulmonary infarction and to the faintest signs of a pathologic condition of the legs, such as a transitory aching in the calf, lasting perhaps only a few hours, a slight change in the color of the skin, a small increase in the firmness of the calf muscles or a tender spot, found only with difficulty, on the back of the lower part of the leg. If phlebographic examination is undertaken in the presence of such signs as these, an accurate diagnosis can usually be obtained in cases in which otherwise one may have merely a faint suspicion that everything is not as it should be. Generally, there will be an absence of opaque filling in one or all of the deep veins of the lower part of the leg, which not only insures the diagnosis but provides objective photographic evidence of the condition. On the other hand, if a normal roentgenogram is obtained—this has occurred in about one fifth of my cases—the possibility of thrombosis is excluded and also all false conclusions respecting the results of therapy instituted on mere suspicion of thrombosis.

TREATMENT OF THROMBOSIS

If it is considered an established fact that the phlebographic examination makes possible the diagnosis of thrombotic disease in its earliest stages, one requisite for successful treatment with heparin has been attained. The other must consist in determining whether a beneficial effect arises from the treatment in cases of the early stages of the disease discovered by such examination.

Theoretically, of course, benefit should ensue. According to what is known, heparin has no direct effect on thrombotic masses which have already entirely filled the vascular lumen and begun to involve the wall. On the other hand, the drug is able to prevent a spread of such masses. Within the thrombosed lower part of a leg changes may be present of such a type that no great effect on them can be expected from treatment with heparin. This, however, is of no consequence, for according to my experience obliteration of the deep veins has no noteworthy significance either for the present or for the future if the process is confined to the lower part of the leg. On the other hand, treatment with heparin can save the veins of the thigh from being occluded. If on the roentgenogram the femoral vein is well defined, there are no thrombotic masses in it and the immediate institution of heparin treatment ought to, and does, prevent the subsequent appearance of such masses.

Treatment of Thrombosis Without the Use of Heparin.—When the practical results of heparin treatment are to be judged, the first step is to get a clear idea of what is the usual fate of patients with thrombosis if such treatment is not undertaken. Relevant to this question is the

material I have at my disposal from 32 cases in which an early stage of thrombosis of the lower part of the leg was phlebographically demonstrated. The patients received no heparin, but in other respects they were treated in the generally accepted way: with elevation of the legs, heat and, in some cases, blocking of the lumbar sympathetic ganglions with procaine hydrochloride. In spite of this therapy the thrombotic process remained localized to the lower part of the leg in only 25 per cent of the cases. In 75 per cent the femoral vein was affected and pronounced phlegmasia alba dolens followed. In 31 per cent the thrombosis became bilateral. In 16 per cent there was extension of the process to the great pelvic veins as well, and in 1 case death ensued on account of thrombosis of the superior mesenteric vein. Further, in

Comparative Data for Cases of an Early Stage of Thrombosis Localized to the Lower Part of the Leg in Which Heparin Was Used and for Similar Cases in Which It Was Not Used.

	Cases in Which Heparin Was Not Used	Cases in Which Heparin Was Used
Total number of cases.....	32	21
Cases in which thrombosis remained localized to the lower part of the leg	8 (25%)	21 (100%)
Cases in which the thrombotic process spread.....	24 (75%)	..
Spread to the thigh, phlegmasia alba dolens.....	24	..
Undoubted spread to pelvic veins.....	5	..
Thrombosis of mesenteric vein.....	1	..
Pulmonary infarction	8	..
Pulmonary embolism	3	..
Thrombosis of the other leg.....	10	..
Cases in which patient died of complication of thrombosis.....	2 (6%)	..
Average confinement to bed after diagnosis of thrombosis, days.....	43	0.7

34 per cent of the cases there were larger or smaller pulmonary infarcts and in 1 case fatal pulmonary embolism. Probably the figure for the latter complications would have been still higher if in cases in which the prognosis appeared especially threatening ligation of the femoral vein had not been employed to stop further advance of the process (table). Thus, great immediate risks, long confinement to bed and considerable later discomfort threaten the great majority of patients once they have beginning thrombosis of the lower part of the leg.

Abortive Treatment of Thrombosis with Heparin.—In striking contrast are the results obtained after the summer of 1940, when in cases of exactly the same type my associates and I began to use heparin. The number of cases observed to date is small (21), but there have been no failures or dubious results in this series. Without exception the temperature and pulse curves, which were commencing to rise, have become normal again within two to four days, and within the same space of time nearly all tenderness on palpation of the lower part of the

leg and all swelling and aching have vanished. The patients have usually been able to get up after another couple of days, provided the primary disease did not prolong their stay in bed. Spread of the thrombosis has not been observed in any case, nor have there been any pulmonary infarcts. As a rule, the patients required administration of heparin for only three to five days and after this time could be regarded as cured. Hence, in these cases, there is some reason for speaking of an abortive treatment of the thrombotic disease (fig. 2).

Dosage: The question of the dosage of heparin to be used in such cases obviously can be answered only after there has been much experience. The daily quantity given undoubtedly ought to be fairly large. At present, I can merely say that in several cases I have succeeded in achieving abortion of the process with such small daily doses as 150 to 200 mg. given in three or four intravenous injections, but since conferring with Jorpes I have seldom given less than 300 mg. daily. Usually the patients receive 100 mg. intravenously three times a day. The first dose is often increased to 125 or, at most, 150 mg. The total quantity employed is between 900 and 1,300 mg. of the ordinary commercial heparin. With this dosage there have been no failures among the cases of thrombosis in which a diagnosis was made early.

Duration of Treatment: A further question to be answered is how many days the heparin treatment is to be continued. I have gradually come to the conclusion that treatment can cease as soon as the pulse curve has become almost normal and the temperature has dropped to within a few tenths of a degree of normal. On the other hand, there is no need to wait until all traces of tenderness on palpation have disappeared. As a rule, it has not been necessary for me to give heparin more than three to five days in cases in which the treatment was abortive. A day or so later the patient is ready to get up.

Treatment of Later Stages of Thrombosis with Heparin.—What has been said refers to what may be called abortive treatment. The use of heparin, however, may well be adopted in certain other circumstances. One must doubtless always count on not being able in all cases to reach a diagnosis as early as is desirable. The onset of thrombotic disease may be either so insidious and imperceptible or so sudden that on the phlebogram even the shadow of the femoral vein will be absent, showing that there is a thrombus in that vein. Ought one to give heparin in such cases?

According to my experience, in the later stages thrombosis may be divided into two types: 1. The thrombus in the femoral vein may be so recent that it is still loosely waving about in the vein. Clinically, this stage is characterized by absence of tenderness on palpation along the course of the vein. On phlebographic examination an extremely small amount of contrast medium may be seen in the femoral vein, in the

form of a mantle shadow, or nothing at all may be visible. In such cases treatment with large doses of heparin should be followed. There is the possibility that the thrombus, which will cease to grow, can be

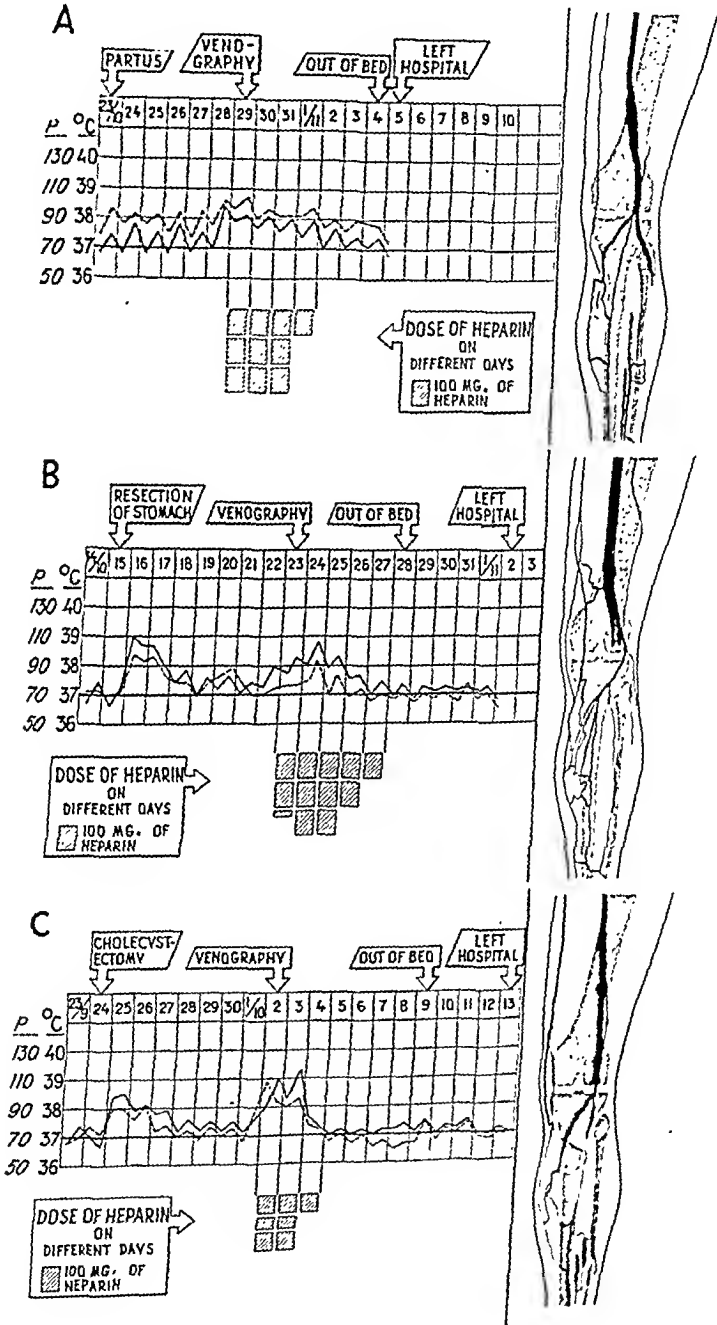


Figure 2

(See legend on opposite page)

dissolved by fibrinolysis in the blood and will disappear. I have a case in which the photographic records seem to indicate that such a dissolution of a thick thrombus took place after a few days of treatment with heparin. Thus, in this type of case, too, the use of heparin serves as a form of

abortive treatment. In such cases the treatment naturally must be continued considerably longer than in the cases of recent thrombosis.

2. Marked tenderness on palpation over the femoral vein and the presence of true phlegmasia alba dolens signify that the thrombus in the femoral vein is already firmly adherent to the wall. No effect from the administration of heparin can therefore be expected in the thrombosed leg. It nevertheless appears to be a logical procedure to introduce such therapy with a view to preventing the thrombosis from becoming bilateral, spreading to the pelvic veins or giving rise to pulmonary complications. On this point my experience is not sufficient to allow of any conclusions.

SUMMARY

For successfully combating thromboembolic disease two measures are necessary: early diagnosis and immediate energetic treatment with heparin.

Phlebography permits of an earlier diagnosis than any other known method. With its aid the first manifestations of the disease in the lower part of the leg can be revealed.

EXPLANATION OF FIGURE 2

Fig. 2.—*A*, abortive treatment with heparin in a case of thrombosis of the left leg. There was a rise in the temperature and pulse curves on the sixth day after a normal delivery. Examination disclosed nothing pathologic except slight tenderness on palpation over the back of the left calf, at the line dividing the top and middle thirds. The phlebogram shows defective contrast filling of the deep venous trunks of the lower part of the leg. The thrombosis is in an early stage and still localized to the lower part of the leg. Immediate treatment with heparin was begun. Three 100 mg. doses were given intravenously for three days and one dose on the fourth day, making a total of 1,000 mg. in four days. On the fourth day all tenderness and swelling were gone, and the pulse and temperature were almost normal. The patient got up on the sixth day and left the hospital the next day. Confinement to bed after diagnosis of the thrombosis was for six days instead of for six weeks, the average period in cases of thrombosis. *B*, abortive treatment with heparin of postoperative thrombosis of the right leg. On the eighth day after operation, there were a rise in temperature and slight swelling of the lower part of the right leg with slight tenderness of the calf. The phlebogram shows thrombosis of all the deep venous trunks of the lower part of the leg and what is probably the head of a waving thrombus in the popliteal vein. Intravenous administration of heparin was begun immediately. On the first day two doses, 125 mg. and 100 mg., were given and on the following three days three 100 mg. doses were administered, or a total of 1,125 mg. in five days. The temperature and pulse rate fell quickly, and the swelling and tenderness receded. The patient got up after five days. The danger of phlegmasia alba dolens or even of pulmonary embolism was averted. *C*, abortive treatment with heparin of postoperative thrombosis of the left leg. In this case somewhat less heparin was given, a total of 475 mg. being administered in three days. The same good result was attained as in the cases previously described.

If in this stage regular treatment with heparin is started, almost ideal results can be expected, for the whole disease often takes an abortive course.

In 21 cases in which the diagnosis of an early stage of thrombosis in the lower part of the leg was confirmed by phlebographic examination, the patient was treated with heparin, 100 mg. three times daily for three to five days. All of the patients recovered and were ambulatory in a few days.

In 32 similar cases in which treatment with heparin was not used, 2 patients died, 3 had pulmonary embolism and 8 pulmonary infarct and in 24 the thrombosis spread to the femoral veins. The average length of confinement to bed was forty-three days.

CONGENITAL LUMBOSACRAL DEFECT

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NORMAN DUREN, M.D.

AND

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The causation and the anatomy of lumbosacral defect have not been well studied, and the assumption is generally made that nothing can be done about the condition. Many of the unfortunate persons with this deformity are of normal mentality. At least 2 persons described in the medical literature, while apparently completely lacking a sacrum, have gone through two pregnancies each. An understanding of their difficulty should be of interest.

The literature on this anomaly lists 41 cases. Since they have been adequately reviewed in recent years, we merely cite the reviews,¹ together with a few isolated cases, and contribute a case that came to our attention at the Children's Hospital in Galveston.

REPORT OF CASES

CASE 1.—A bright looking 9 year old boy was admitted to the orthopedic service by one of us (N. D.) in November 1940 (fig. 1). He was able to sit up and drag himself about by the use of his arms but had no use of his voluntary muscles below the thorax. The head appeared moderately hydrocephalic. The neck was short and the chest large, barrel shaped and muscular. The thoracic spine was lordotic above and kyphotic below. Spinous processes were missing on and below the twelfth thoracic vertebra. The abdomen tapered abruptly. The sacrum could not be palpated, and the pelvis was narrow. The legs were flexed sharply on the thighs, the heels touched, and the soles faced upward and inward. A web of skin extended from the posterior surface of the thighs to the calves, obliterating the popliteal spaces. The symphysis pubis was present, and both the anus and the genitalia appeared normal.

The heart and lungs appeared to function normally. Incontinence of urine and feces was present. Muscle was absent or completely atrophied in the limbs, and no reflexes were obtained. Cutaneous sensation was normal. While he felt neither pain nor discomfort from his condition, pain could be elicited on vigorous manipu-

From the University of Texas School of Medicine.

1. Hamsa, W. R.: Congenital Absence of Sacrum, *Arch. Surg.* **30**:657-666 (April) 1935. Girard, P. M.: Congenital Absence of Sacrum, *J. Bone & Joint Surg.* **17**:1062-1064 (Oct.) 1935. Zeligs, I. M.: Congenital Absence of Sacrum, *Arch. Surg.* **41**:1220-1228 (Nov.) 1940.

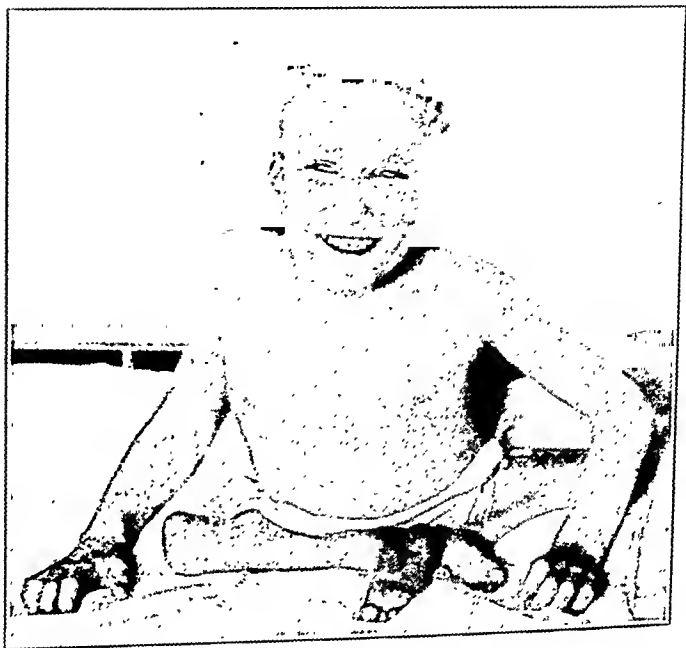


Fig. 1.—A 9 year old boy with congenital lumbosacral defect.



Fig. 2.—Roentgenogram of pelvic defect showing medial articulation of the twelfth ribs and of the iliac crests. Lumbosacral vertebrae are missing.

lation. The skin showed no trophic disturbance. The result of a Wassermann test was negative.

A roentgen examination was made by one of us (J. C. R.). The large cranial vault showed no widened sutures or evidence of pressure on the sella tureica. The spines from the fifth cervical to the second thoracic vertebra were bifid. The body of the twelfth thoracic vertebra was absent, yet the ribs, derived from its transverse processes in early development, nearly articulated across the mid-line (fig. 2). All vertebrae below this were missing or at least did not show any ossified remnants. The iliac bones articulated with each other. The limb bones were normal except for a small defect of the right fibula.

This boy came from a family of 8 members, all of whom were normal. His deformity had been present since birth. It was felt that nothing could be done for him, and after examination he went home.

CASE 2.—In 1932 we obtained locally a 60 mm. fetus presenting the same external picture as the boy just described. Nothing was known of the parentage.



Fig. 3.—Lumbosacral defect in a 60 mm. fetus.

The fetus showed a normally developed head and trunk to the middle lumbar region, but from there it quickly shrunk to a size suitable to a much smaller fetus, with all parts apparently well formed (fig. 3). The skin showed some edema but no vascular congestion.

A dissection of the back showed normal development of all the extensor muscles and vertebrae back to the last thoracic segment. In the lumbar region the muscles continued intact to the level of the constriction. At this level all muscles except the extensors showed traumatic distortion, and muscles lateral to the centrums were ruptured, as the lower lumbar wall was telescoped into the upper wall for a distance of one segment. The defect continued ventrally to the umbilical cord. Below the fold all muscle again became normal but reduced in volume.

Serial transverse sections were prepared from upper lumbar levels downward (fig. 4). The first, second and third vertebral arches showed progressive spina bifida similar to the normal arches of the lower sacral segments. This shallow

trough continued through the lumbar, sacral and coccygeal regions, all segments being present in cartilage. The pelvic girdle and limb cartilages were normal. The fourth lumbar centrum began normally but tapered out caudally to a thin wedge lacking perichondrium. Ventral to the fourth lumbar centrum lay the fifth. It started cranially as a long irregular wedge without perichondrium and became normal caudally. Its vertebral arch was sheared off on one side and lay wedged into the vertebral notch of the one above. On the other side it pressed the centrum above it, causing a kink in the vertebral canal and torsion of the

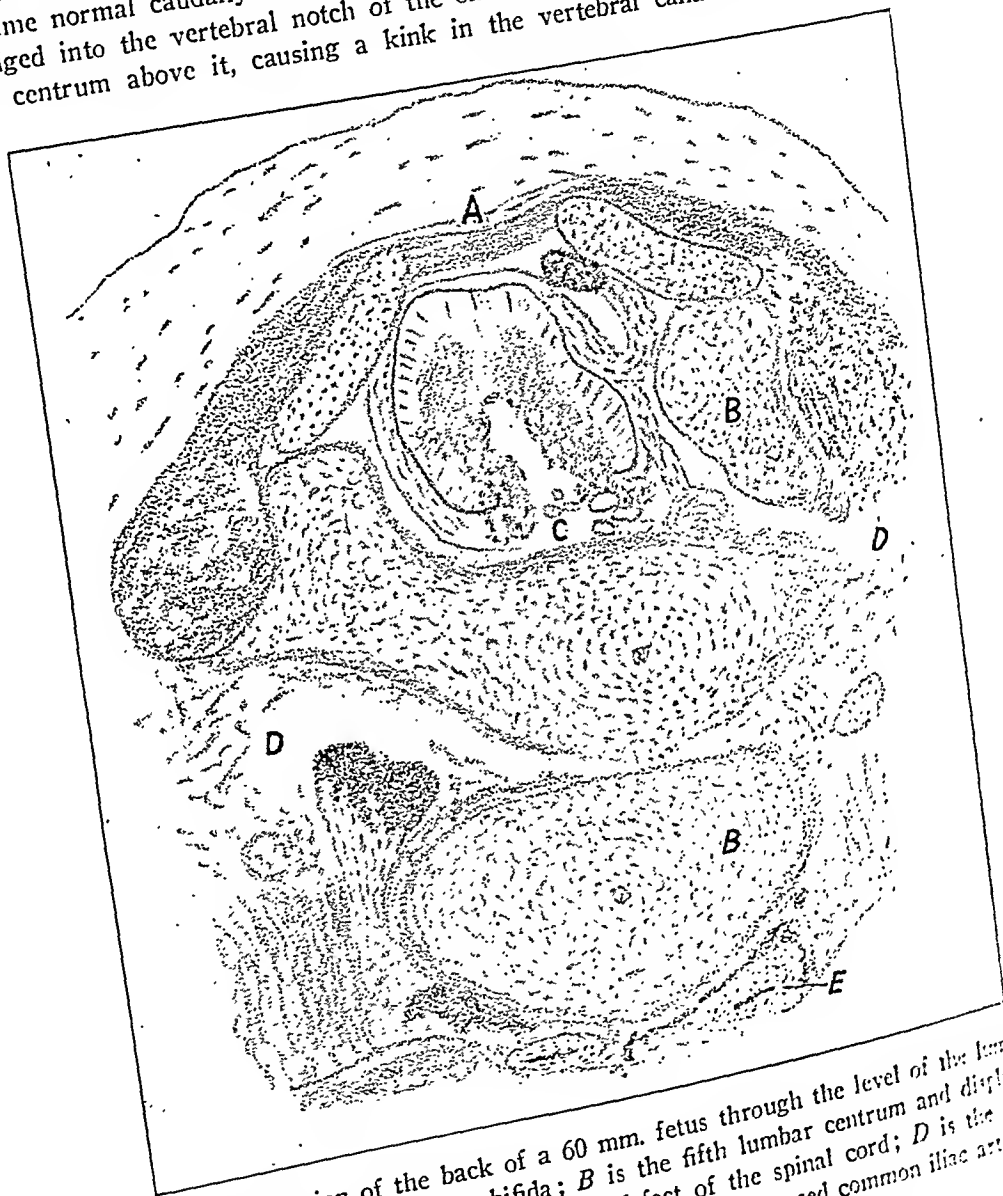


Fig. 4.—Section of the back of a 60 mm. fetus through the level of the lumbar sacral defect. *A* is the spina bifida; *B* is the fifth lumbar centrum and displaced arch; *C* is the beginning of the ventral defect of the spinal cord; *D* is the level of rupture of muscle and nerves; *E* indicates the compressed common iliac arteries.

spinal cord. The sacral centrams lay in line with that of the fifth lumbar. Each centrum contained a segment of the notochord. The spinal cord filled the open trough nearly to the end of the vertebral column and was so thick that it rose above the crests of the spinal arches. In the upper lumbar levels it showed a patchy ependyma even where the rest of the

section was normal. At the level of the fault, the floor of the canal dropped, and the dura attached to the fifth vertebra at the foramina pulled downward on the cord. The wedgelike end of the fourth lumbar centrum spread the ventral half of the cord and penetrated into the neural canal. Immediately below this the ventral gray matter and lateral and ventral funiculi were completely disintegrated, not by atrophy or necrosis but by trauma. The scattered cells still stained normally.

The aorta bifurcated just above the fault line after the mesenteric and renal arteries branched off. Under the last lumbar vertebral body the common iliac arteries were compressed almost to obliteration, though under full arterial pressure they had apparently functioned to some extent. Most of the blood here was destined for the placenta, and this compression may easily have been the cause of death. All viscera were perfectly developed.

An explanation of this developmental defect goes back to a stage when the embryo was 4 to 15 mm. in length. During this period the sclerotomes are formed and begin to chondrify. There was evidence of developmental arrest of the arches below the thorax, even though other segmental mesodermal derivatives were normal. From some unknown cause the plane separating the fourth and fifth lumbar segments was neither vertical to the axis nor strictly transverse. No difficulty was experienced until the large extensor muscles of the back began to contract. Under the strain, the vertebrae were displaced along the fault plane, perichondrium was gradually stripped, the umbilical vessels were compressed, and the spinal cord was broken. The process was gradual, including limitation of blood to the legs and loss of cerebral control of the voluntary musculature. This, of course, includes the striated sphincters of the anus and urethra. It in no wise affected the smooth muscles of the gut or urogenital tract. The sympathetic chain was intact. The dorsal roots and spinal ganglia were intact, except for one pair, together with the dorsal funiculi and the dorsal half of the gray matter. In this way afferent tracts were preserved in part, even pain and temperature fibers for a couple of segments below the injury.

COMMENT

It is probable that this explanation when adapted to various levels, various angles or degrees of depression and different intervals of time may be applied to the lumbosacral defects described in the literature. In all of the reported cases, the afferent tracts were fairly well preserved, while the voluntary motor controls were impaired or missing. There was incontinence of feces and urine. The pelvic girdle developed without vertebral support. Spina bifida and other vertebral defects were commonly associated with vertebral termination, generally in the lumbar region. From a developmental standpoint it seemed impossible to have complete agenesis of somites or of any part of them, because both epaxial and hypaxial myotomes were developed. Any asymmetric segmental development of a single somite would produce an oblique intervertebral plane. Since the notochord was present in thoracic levels, it must have been continuous with the primitive knot from which it originated. If sclerotomes had not developed, the neural crest would not have been

separated into ganglions, and the sympathetic chain, which became separated ventrally from it, could hardly have been formed. Suppression of primordiums originally present offers a more reasonable explanation. The idea that the defect was purely traumatic and not based on an embryonic fault is not true. It does not account for the peculiar angle of the intervertebral plane or for the spina bifida generally present. A failure of the cartilaginous elements below the defect to ossify would present itself in a child as lack of skeletal support and would not show in a roentgenogram. If the final compression did not occur until the spinal cord was drawn well up into the vertebral canal, the injury would not involve so many neural segments so completely. The apparent lack of somatic muscles may well be due to failure of these muscles to develop beyond a fetal stage for lack of functioning reflex paths.

In conclusion, it seems possible that congenital lumbosacral defect may be traced back to a simple vertebral defect at the stage of chondrification or the later stage of ossification. This simple defect during the development of extensor functions of the back may be aggravated to present a picture of complete somatic dysfunction or atrophy below the level of the fault.

SUMMARY

Congenital absence of lumbar and sacral vertebrae is compatible with life and with considerable visceral function. It is associated with other skeletal anomalies, with loss of somatic motor controls below the upper level of the anomaly, with preservation of afferent paths and with general atrophy or undevelopment of muscle in the lower part of the body and limbs. It is traced back to the stage at which vertebral primordia are laid down and consists in faulty intervertebral articular planes. The extensor muscles dislocate the centrum along an oblique plane, the cartilages thereby compressing the aorta, rupturing muscles and some nerves and compressing or destroying part of the ventral half of the cord.

A 9 year old boy is compared with a 60 mm. fetus, both having similar defects.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1940

THE FIRST OF A NEW SERIES OF REVIEWS WHICH WILL BE PREPARED
BY AN EDITORIAL BOARD OF THE AMERICAN ACADEMY
OF ORTHOPAEDIC SURGEONS

PREFACE

Realizing the value of a more comprehensive review of the orthopedic literature than was being published, the American Academy of Orthopaedic Surgeons, through its executive committee, decided to sponsor a new "Progress in Orthopedic Surgery" and authorized the editorial committee to proceed in its preparation for the literature of 1940. An editorial board of twenty-three orthopedic surgeons representing twenty different centers was appointed by the president of the Academy, with the chairman of the editorial committee as the chairman of this editorial board. The members of the board are as follows:

Dr. LeRoy C. Abbott, San Francisco, Professor of Orthopedic Surgery, University of California Medical School

Dr. Walter P. Blount, Milwaukee, Attending Orthopedic Surgeon, Columbia, Milwaukee Children's and Milwaukee County Hospitals

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Dr. H. Earle Conwell, Birmingham, Ala., Consulting Orthopedic Surgeon, Employees' Hospital of Tennessee Coal, Iron and Railroad Company (Fairfield, Ala.)

Dr. Frank D. Dickson, Kansas City, Mo., Chief of Orthopedic Service, St. Luke's, Kansas City General and Wheatley-Provident Hospitals, Professor of Clinical Surgery, University of Kansas School of Medicine

Dr. Rex L. Diveley, Kansas City, Mo., Associate Chief of Orthopedic Service, St. Luke's, Kansas City General and Wheatley-Provident Hospitals

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Dr. A. Bruce Gill, Philadelphia, Professor of Orthopedic Surgery, University of Pennsylvania School of Medicine

Dr. J. Hiram Kite, Atlanta, Ga., Surgeon in Chief, Scottish Rite Hospital for Crippled Children (Decatur, Ga.)

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Dr. Philip Lewin, Chicago, Associate Professor of Bone and Joint Surgery, Northwestern University Medical School; Professor of Orthopedic Surgery, Cook County Graduate School of Medicine

Dr. I. William Nachlas, Baltimore, Associate in Orthopedic Surgery, Johns Hopkins University School of Medicine

Dr. Winthrop M. Phelps, Baltimore, Medical Director, Children's Rehabilitation Institute; formerly Professor of Orthopedic Surgery at Yale University School of Medicine

Dr. Robert D. Schrock, Omaha, Professor of Orthopedic Surgery, University of Nebraska College of Medicine

Dr. Alfred R. Shands Jr., Wilmington, Del., Chairman of the Editorial Board, Medical Director of the Alfred I. duPont Institute of the Nemours Foundation; Visiting Professor of Orthopedic Surgery, University of Pennsylvania School of Medicine

Dr. Alan DeForest Smith, New York, Surgeon in Chief, New York Orthopedic Hospital; Clinical Professor of Orthopedic Surgery, Columbia University College of Physicians and Surgeons

Dr. J. Spencer Speed, Memphis, Tenn., Surgeon in Chief, Willis C. Campbell Clinic; Professor of Orthopedic Surgery, University of Tennessee College of Medicine

Dr. Arthur Steindler, Iowa City, Professor and Head of Department of Orthopedic Surgery, State University of Iowa College of Medicine

Dr. Loring T. Swaim, Boston, formerly Chief of Medical Staff, Robert Breck Brigham Hospital; Instructor in Orthopedic Surgery, Harvard Medical School

Dr. J. Warren White, Greenville, S. C., Surgeon in Chief, Shriners' Hospital for Crippled Children

Dr. Philip D. Wilson, New York, Surgeon in Chief, Hospital for Ruptured and Crippled; Clinical Professor of Orthopedic Surgery, Columbia University College of Physicians and Surgeons

The chairman of the editorial board divided orthopedic surgery into 20 subjects, the complete list of which was published in the July issue of the ARCHIVES OF SURGERY (p. 168). Each editor was assigned a subject, to which in most instances either he or the group he represents has made outstanding contributions in the past. The titles of 1,794 articles of orthopedic interest were selected from the *Quarterly Cumulative Index Medicus* for 1940. These were then grouped according to subject as accurately as possible from the titles and sent to the proper editor for review. Each editor was instructed to report only on articles which appeared to represent definite progress or to contain information of unusual interest. The total number of articles reviewed in the final report is 687. It is to be regretted that owing to the European war it has been impossible to obtain many of the foreign publications.

Some subjects, such as "Fresh Fractures and Dislocations," have a more voluminous literature than others; accordingly, these sections are longer. An attempt has been made to adopt a uniform style in the presentation of the material. However, in this first publication, with 20 sections being prepared for the first time in as many different centers, this has been only partly accomplished. Some sections have had more editorial comments than others. These are the reactions of the individual editors to the articles being reviewed. If the reader or the editor

of any article does not agree with the editorial comment, the editorial committee hopes that he will think of the remark as only one man's impression and as in no way representing the opinion of the entire editorial board.

In the preparation of the material, the following orthopedic surgeons acted as assistants to the editorial board:

For Dr. Abbott:	Dr. J. B. DeC. M. Saunders, San Francisco Dr. F. C. Bost, San Francisco Dr. K. O. Haldeman, San Francisco Dr. R. Soto-Hall, San Francisco
For Dr. Colonna:	Dr. W. A. Klein, Oklahoma City
For Dr. Ghormley:	Dr. H. H. Young, Rochester, Minn.
For Dr. Shands:	Dr. G. Newton Boice, Wilmington, Del. Dr. W. Richard Ferguson, Wilmington, Del. Dr. W. B. Sheppard, Wilmington, Del. Dr. Raymond P. Thornhill, Wilmington, Del.
For Dr. Smith:	Orthopedic staff of New York Orthopædic Dispensary and Hospital
For Dr. Steindler:	Dr. J. L. Marxer, Iowa City Dr. L. A. Williams, Iowa City Dr. M. Rosenbusch, Iowa City Dr. L. J. Barron, Iowa City Dr. A. L. Freedman, Iowa City Dr. J. S. Mule, Iowa City Dr. G. Miyakawa, Iowa City Dr. T. J. Greteman, Iowa City
For Dr. Swaim:	Dr. George J. Baer, Boston Dr. John P. Stump, New York
For translation of Latin- American articles:	Dr. Alberto Inclán, Habana, Cuba

The ARCHIVES OF SURGERY kindly agreed to allow this new "Progress in Orthopedic Surgery" to replace the old "Progress," published for many years in its pages. It is sincerely hoped that this "Progress" during its first year may receive the approval and good will of its readers and prove to be a publication of great usefulness to all interested in the problems of orthopedic surgery.

(Signed) The Editorial Committee of the
American Academy of Orthopaedic Surgeons.

E. BISHOP MUMFORD, M.D.

REX L. DIVELEY, M.D.

A. R. SHANDS JR., M.D., Chairman.

I. CONGENITAL DEFORMITIES

General Considerations.—The study of human fetal malformations includes not only the gross anomalies which are called monsters but also every possible disturbance of structural and functional development. Teratology is the name given this science, and according to Savage and Dorman¹ in an interesting review of the subject, it is derived from the Greek *τέρας*, meaning monster. "Congenital" means that the anomalies were present at birth; "hereditary," that they were received through the inheritance of defects of ancestors.

Mall taught that monsters were produced by external influences on normal ova. Piette² gives another explanation. He states that it appears possible that most spontaneous abortions, stillbirths, monstrosities and malformations are due to the fertilization of dying ova, which have apparently a short span of life.

He writes:

It seems possible that a monstrosity or a malformation is the result of the fertilization of a dying ovum by a normal spermatozoon or, less likely, the result of the fertilization of a healthy egg by a dying spermatozoon. The first possibility appears more likely, because the ovum, according to the prevailing current concept, has a very limited span of life, some forty-eight hours or less, whereas the life span of a spermatozoon is seventy-four hours. Watching any protozoon die under a microscope—an ameba or a flagellate, for instance—one notices that it does not die at once and in all parts at the same time. Some parts survive much longer than the others. If, therefore, an egg is impregnated by a spermatozoon at, say, forty hours after extrusion, when it is on its last—is almost dead—a grave malformation may result. If the egg is but slightly damaged by the process of its rapidly approaching senility one may expect a slight malformation of one part of the body of the fetus. If the ovum was all but dead at the time of fertilization one might expect not only a malformation but a dead fetus unable even to go through the stages of intrauterine development.

Savage and Dorman¹ report that in 8,365 deliveries in the department of obstetrics of the University of Maryland School of Medicine only 41 (0.49 per cent) anomalies of the types which are usually seen by the orthopedic surgeon were observed. Thirty-two of these were examples of polydactylism, and 9, of clubfoot.

1. Savage, J. E., and Dorman, J. W.: Congenital Anomalies. *Bull. School Med. Univ. Maryland* 25:23-30 (July) 1940.

2. Piette, E. C.: Possible Cause of Malformations and Spontaneous Abortions. *Illinois M. J.* 77:375-376 (April) 1940.

The Klippel-Feil Syndrome.—A complete review of articles on congenital synostosis of the cervicothoracic vertebrae (the Klippel-Feil syndrome) has been made by Rechtman and Horwitz.³ After summarizing about 83 articles, they report 3 cases. The syndrome is characterized first by shortness of the neck. The head appears to be directly implanted on the trunk. The neck is broad, and the chin approximates and may even rest on the sternum. Occasionally, the trapezial muscles stretch winglike from the mastoid processes to the shoulders, suggesting the name of pterygium colli or web neck. In addition, the syndrome is characterized by low implantation of the hair line and limitation of movements of the head and neck. These movements are painless, the deficiency being purely mechanical. The secondary characteristics are: (1) scoliosis or kyphoscoliosis, (2) elevation of the scapulas, (3) descent of the nipples of the breast and (4) disproportion between the length of the extremities and the trunk, which gives the patient an almost simian appearance. These characteristics may occur in whole or in part and with varying degrees of intensity.

From the standpoint of pathologic anatomy the main changes in the cases described by Feil were a reduction in the number of cervical vertebrae, which were fused in whole or in part, the presence of a superior cervical spina bifida and an elevation of the thoracic cage with formation of a cervical thorax, which was more or less developed. The diagnosis is easily confirmed by roentgenography, which is necessary to rule out more serious lesions of the neck.

There is no therapy for the cervical deformity itself. The prognosis is good. Associated deformities, such as scoliosis, torticollis, clubfoot and clubhand, should be corrected.

Cleidocranial Dysostosis.—This may be defined as a congenital anomaly which may or may not be hereditary and which consists of a material defect in the clavicles without attempted repair and a large brachycephalic skull with a tendency for the fontanels and sutures to remain patent. Such a description is given by Miles,⁴ who has made a careful review of the literature and has added 6 cases of his own, 5 of which were in the same family.

Meckel published in 1760 what is probably the first record of a human being born without clavicles. Pierre Marie and Paul Sainton

3. Rechtman, A. M., and Horwitz, M. T.: Congenital Synostosis of the Cervicothoracic Vertebrae (Klippel-Feil Syndrome), *Am. J. Roentgenol.* **43**:66-73 (Jan.) 1940.

4. Miles, P. W.: Cleidocranial Dysostosis: Survey of Six New Cases and One Hundred and Twenty-Six from Literature, *J. Kansas M. Soc.* **41**:462-468 (Nov.) 1940.

in 1898 named the condition *la dysostose cléidocranienne héréditaire* and listed four characteristics: aplasia of the clavicles, brachycephaly, persistent fontanels and hereditary transmission. Miles⁴ says that the incidence of this rare condition is not evidently increasing and presents few or no medical problems. When a patient with this condition consults a doctor, however, he asks many questions. "It is certainly comforting to know," writes Miles, "that anticipated children will not be abnormal mentally and that they have a 50 per cent chance to be normal physically." In his review of 132 cases he found that 47 per cent of these cases were familial, the deformity appearing in two or three generations, nearly all members of which were affected. Fifty-three per cent were isolated nonhereditary cases.

Marshall and Wulff⁵ call attention to the deformity of the pelvis due to cleidocranial dysostosis. This anomaly is characterized by delayed or incomplete ossification of the skeleton, usually affecting most of the bones formed from membrane. They observed a mother and her child who had many deformities due to this dysostosis. The mother had a deformed pelvis, and the paper deals with the obstetric problem which the distortion presented. [Ed. Note: Pelvic deformity is seldom if ever thought of in connection with cleidocranial dysostosis.]

Absence of the Pectoral Muscles.—Brown and McDowell⁶ say that more than 300 cases of congenital absence of the pectoral muscles have been reported but that the true incidence of the lesion is unknown because the deformity is often not obvious and is discovered only by careful examination of the area about the shoulder. The lesion is usually not disabling. They report 2 cases in which this deformity was found associated with syndactylism.

Deformity of the Upper Extremity.—Stein and Bettmann⁷ present a rare malformation of the arm in a woman of 52. She had a giant scapula, a double humerus, two radiuses, three ulnas and three hands with sixteen fingers. A similar case cannot be found in the literature. The three hands could perform useful tasks alone or in combination, since they had muscle groups of normal shape and number. The hands could be flexed and extended independently, making all known combinations of flexion and extension possible.

5. Marshall, C. J., and Wulff, B. I.: Deformed Pelvis Due to Cleidocranial Dysostosis, *Am. J. Obst. & Gynec.* 39:136-137 (Jan.) 1940.

6. Brown, J. B., and McDowell, F.: Syndactylism with Absence of the Pectoralis Major, *Surgery* 7:599-601 (April) 1940.

7. Stein, H. C., and Bettmann, E. H.: Rare Malformation of Arm: Double Humerus with Three Hands and Sixteen Fingers, *Am. J. Surg.* 50:336-343 (Nov.) 1940.

Congenital Dislocation of the Elbow.—Mauck and Butterworth⁸ report 2 cases of bilateral congenital dislocation of the head of the radius. This is a relatively rare condition. They operated on one of the arms to reduce the dislocation and tried to hold the head of the radius in position with a sling of fascia lata round the radial neck. When the elbow was extended during the operation, the fascia lata was torn. The head could not be held in position because it was convex and the coronoid fossa ill formed. The head of the radius was removed. They conclude that the pathologic condition is such that any operation other than removal of the head is not satisfactory.

Syndactylism.—Snedecor and Harryman⁹ report the Jackson White family to confirm the statement of Edwards that syndactylism is a stigma of degeneration occurring in persons of weakened intelligence. This family is a mixture of English, Hessian, Indian and Negro. During the Revolution an English sea captain named Jackson was commissioned to bring over a cargo of women for the Hessian soldiers garrisoned in New York. In the course of events he bought or shanghaied a boatload of female derelicts off the streets of London and later added some Negresses from the West Indies. After the war these with some abandoned Hessians and Indians were driven to the Ramapo Mountains, where they lived undisturbed by civilization for a hundred and fifty years. Syndactylism and polydactylism have been traced back for four generations. They conclude that the contributing factors causing this defect to appear were inbreeding, low intelligence, dietary deficiencies and poverty in an outcast environment for many generations. This condition occurred in over 50 per cent of the progeny.

Haas¹⁰ reports 2 cases of complete bilateral syndactylism. The patients were brother and sister. The mother had had severe syndactylism of both hands. These deformities are congenital and represent an atavistic trait. Restoration of six fingers with their corresponding metacarpal bones was secured on both hands in the patient whose case is described in detail.

Seventy-three patients with congenital webbing of the fingers have been studied by MacCollum.¹¹ In discussing the anomaly embryologically he states that between the sixth and the seventh week of fetal

8. Mauck, H. P., and Butterworth, R. D.: Two Cases of Bilateral Congenital Dislocation of the Head of the Radius, *J. A. M. A.* **114**:2542-2543 (June 29) 1940.

9. Snedecor, S. T., and Harryman, W. K.: Surgical Problems in Hereditary Polydactylism and Syndactylism, *J. M. Soc. New Jersey* **37**:443-449 (Sept.) 1940.

10. Haas, S. L.: Bilateral Complete Syndactylism of All Fingers, *Am. J. Surg.* **50**:363-366 (Nov.) 1940.

11. MacCollum, D. W.: Webbed Fingers, *Surg., Gynec. & Obst.* **71**:782-789 (Dec.) 1940.

life the finger buds grow more rapidly than any other portion of the appendage. Because the growth of the finger buds is so much more rapid than the tissue between them, the webs become less and less marked until finally the only remnants are the webs that exist on the palmar surface of the normal hand. If there is a temporary arrest in development during the seventh or eighth week of fetal life, this disproportionate rate of growth will not occur. It is then quite possible for two or more fingers to be momentarily retarded in growth and to remain united by their webs. Later in fetal life, growth both of the finger buds and of the webs between them takes place at an even rate so that at birth, even though the fingers may have attained proper length, the webs will still be present and of the same length as the fingers.

The sex ratio in MacCollum's series was the same as in most others—66 per cent males to 34 per cent females. Forty-eight per cent showed involvement of both hands. [ED. NOTE: This percentage is the same as for congenital clubfoot.]

He has found that the best time for operation when the web holds the fingers tightly together is between 2 and 5 years. To operate on a baby with tightly fused fingers in the first two years of life exacts the ultimate of patience from the surgeon both during the operation and later as he daily tries to bandage tiny wriggling fingers. Frequently a successful operative result is ruined by lack of cooperation from the patient during the important period of splinting, exercise and massage. If the web between the fingers is loose enough to fan out as the fingers are separated, it is advisable to postpone correction until the child is old enough to cooperate with the dressing, exercises and massage, all of which are necessary to provide a good operative result. The best time is between 6 and 7 years.

The operation he recommends utilizes two V-shaped flaps, one from the dorsum and one from the palmar surface, to line the commissure between the fingers. The denuded areas on the fingers are covered with thick razor grafts from the thighs or with full thickness grafts. He stresses the importance of careful dressing and uniform splinting of these fingers combined with proper physical and occupational therapy must be carried out for a prolonged period in order to produce a satisfactory result.

Arachnodactyly.—Olcott¹² says that arachnodactyly, or Marfan's syndrome, is characterized by elongation and narrowness of the long

12. Olcott, C. T.: Arachnodactyly (Marfan's Syndrome) with Severe Anemia. *Am. J. Dis. Child.* 60:660-668 (Sept.) 1940.

bones, particularly those of the metacarpus, the fingers and the toes. It was named *dolichostenomélie* (long narrow limbs) by Marfan in 1896. It is now more generally called arachnodactyly (spider fingers), a term first used by Achard in 1902. Several observers have found a definite familial incidence of arachnodactyly. The condition is important chiefly because of serious lesions that accompany the bony abnormality. As is mentioned by Lloyd and Burch, dislocation of the lenses of the eyes occurs in at least half of the cases. Spinal curvature was reported first by Méry and Babonneix and is usually present, being found especially as kyphoscoliosis. These spinal deformities are generally attributed to muscular weakness rather than to bony deformity.

Olcott reports the case of a girl 15 years and some months old who had arachnodactyly, kyphoscoliosis, congenital cardiac anomalies and cloudiness and displacement of the lenses of the eyes. There were also congenital dislocation of the hip, misplacement of a kidney and atrophy of the frontal lobes of the brain. The patient had severe anemia of the secondary type. Evidence is presented indicating that arachnodactyly and the anomalies associated with it are due to disturbance of the development of the middle germ layer.

Rambar and Denenholz¹³ report a case of arachnodactyly with autopsy including histologic examination of the eye. They state: "It is felt that this condition is probably one which occurs in the early embryonic stage, and may be considered an example of defective anlage."

Bean and Fleming¹⁴ give the differential points between arachnodactyly and status dysraphicus, which is like syringomyelia. Patients with the second condition are displayed as the "living skeleton" and the "thin man" at the circus. The authors report a case in which there was an unusual cyst arising from the linings of the sacral canal, a form of spina bifida not heretofore reported, resulting in an equally rare condition causing cephalopelvic disproportion in pregnancy.

Hereditary Edema of the Lower Extremity.—An interesting case of hereditary edema of the legs, or Milroy's disease, has been reported by Rosenberg.¹⁵ This is a rare condition in itself, and in this case it was still more interesting because there were associated congenital anomalies not previously reported. These were: retention of the

13. Rambar, A. C., and Denenholz, E. J.: Arachnodactyly: Report of a Case with Autopsy, Including Histologic Examination of the Eye, *J. Pediat.* **15**:844-852 (Dec.) 1939.

14. Bean, W. B., and Fleming, J. G.: Arachnodactyly: Report of Case Complicating Pregnancy at Term, *Ohio State M. J.* **36**:155-160 (Feb.) 1940.

15. Rosenberg, W. A.: Hereditary Edema of Legs (Milroy's Disease) Associated with Other Congenital Anomalies, *Arch. Dermat. & Syph.* **42**:1113-1121 (Dec.) 1940.

deciduous teeth, the presence of six toes on the left foot, congenital strabismus with amblyopia of the left eye and dystrophy of the hair.

Absence of the Tibia.—Dennison¹⁶ reports a case of apparent congenital absence of the tibia, in which some ossification later took place. A deformed fibula was present. He operated on the knee to impact the fibula between the femoral condyles and was perturbed to find an apparently normal tibial head, articulating in the usual manner with the femoral condyles. Later roentgenograms showed a center of ossification for the tibia. He makes a plea to withhold amputation in cases of this type until a more prolonged investigation is made.

[ED. NOTE: Total absence of a long bone is more rare than partial absence. The literature has taught for some years that a bone is not to be considered totally absent until after the normal time for the appearance of centers of ossification for that bone has elapsed.]

Clubfoot.—Kite¹⁷ in a paper on congenital clubfoot repeats the admonitions given previously, urging physicians who deliver babies with this deformity to send them for treatment early. He states that most clubfooted babies have been delivered by physicians and not midwives, and yet many physicians still do not advise the parents to get early treatment for clubfooted babies. However, progress is being made as a result of the educational campaign for early treatment. The average age of 24 new clubfooted patients treated during 1923 was 31.5 months, while the average age of 25 new patients received in 1938 was only 10 months.

[ED. NOTE: Fifteen years ago one of us (J. H. K.) described in detail a method of correcting clubfoot by casts and wedgings and recommended that in all early cases conservative treatment be used and that forcible manipulation with the patient under an anesthetic and operation be used only for the older patients. He thought that the family physicians could follow these instructions and treat clubfooted babies early. Experience has shown that the family physicians and some of the general surgeons do not have the necessary trained help and equipment to carry on this work successfully; hence he now advises that all clubfooted patients be sent to orthopedic surgeons who specialize in treating this anomaly. He finds that in many cases in which the condition has been only partially corrected by the first treatment correction is more difficult because of the adhesions which follow this treatment and that the time required to correct these relapsed in:

16. Dennison, W. M.: Delayed Ossification of Tibia in Apparent Congenital Absence, *Brit. J. Surg.* 28:101-105 (July) 1940.

17. Kite, J. H.: Some Comments on the Treatment of Congenital Clubfoot, *J. M. A. Georgia* 29:212-216 (April) 1940.

is longer than for untreated feet. He now advises that treatment be given early and only by an orthopedic surgeon.]

Cozen and Greene¹⁸ report 89 cases of congenital equinovarus in which treatment was by various methods and conclude that improvement of the deformity can be obtained by almost any form of treatment and that the final results are satisfactory but that there is a tendency for the deformity to recur. Shoes were of minor importance in the treatment, and it is felt that in the past too much reliance has been placed in them.

Garceau¹⁹ describes an operation which he found helpful in those cases in which clubfoot recurs after apparently adequate conservative treatment. He thinks that the anterior tibial muscle is the mechanical factor producing the recurrence. He describes an operation in which he frees the attachment of the anterior tibial muscle at its insertion on the medial side of the foot and transplants the tendon into the proximal end of the fifth metatarsal bone. After this the foot is kept in casts for eight weeks, and during this time the ankle is wedged in dorsiflexion until the equinus deformity is well corrected. This operation was performed on 56 feet with no bad effects from the sacrifice of the anterior tibial tendon and with satisfactory end results in 93 per cent of the feet.

[ED. NOTE: Probably as long as ten years ago, Dr. John Royal Moore at the Shriners' Hospital for Crippled Children in Philadelphia showed one of us (J. H. K.) patients on whom he had done this same operation. He used it to gain correction in patients being treated for the first time as well as in those in whom there was recurrence. He noted that he had later to replace the anterior tibial tendon in some cases, as it overcorrected the foot. This work was never published.]

Anomaly of the Fifth Toe.—Galland²⁰ describes the deformity of the fifth toe in which this digit overlaps the adjacent fourth toe. He says that it is due to the presence of an abnormal interdigital web, which tends to produce a recurrence after correction of the deformity. He devised an operation for this condition and says that the skin incision constitutes the basic factor in the operation. The incision is made in the shape of an obtuse angle Z on the dorsum of the foot. Through this incision, all resistant tissue is cut; the operation includes a capsulotomy and a tenotomy. Only the skin is closed, and this falls together in a straight line. The toe is held in slight overcorrection with adhesive tape for six weeks.

18. Cozen, L., and Greene, W.: Congenital Equinovarus, *West. J. Surg.* **48**:697-706 (Nov.) 1940.

19. Garceau, G. J.: Anterior Tibial Tendon Transposition in Recurrent, Congenital Clubfoot, *J. Bone & Joint Surg.* **22**:932-936 (Oct.) 1940.

20. Galland, W. I.: Operation for Correction of Congenital Overlapping of Fifth Toe, *Bull. Hosp. Joint Dis.* **1**:93-98 (Oct.) 1940.

II. CONGENITAL DISLOCATION OF THE HIP

Causation.—Storck²¹ believes that a hereditary anomalous shape of the uterus may be an endogenous factor in the production of certain congenital deformities, such as dislocation of the hip and torticollis, because it may necessitate deviations in the position of the fetus. As twin pregnancy is a hereditary trait transmissible through the male, he maintains that congenital dislocation of the hip also may be transmitted through the male.

[ED. NOTE: It seems possible that dislocation of the hip in some cases is a secondary deformity due to a restrained position of the fetus within the uterus. Undoubtedly, however, there are numerous cases of primary deformity, due to an extremely early faulty growth of the fetus. In these cases there may be extreme abnormality in the structures of the hip which cannot be explained by mechanical laws, accompanied by other severe deformities, such as arthrogryposis.

Furthermore, in only about 12 per cent of cases has dislocation been proved hereditary. All observations and research are to be welcomed, but certainly at the present time the etiology of congenital dislocation of the hip is obscure.]

Experimental Dislocation of the Hip.—Dislocation of the hip was produced by Whiston²² in chicks less than 1 day old by prolonged traction without immediate injury to the blood supply of the capsule or the ligamentum teres femoris. They were killed later at intervals up to thirty-two weeks, and careful examination of the dislocated hips was made to determine the pathologic changes attendant on the dislocation.

The ligamentum teres was elongated and thickened by a process of fibrous hyperplasia. [ED. NOTE: In man the ligamentum teres is sometimes broad and thick, sometimes thin, atrophic and weak and sometimes entirely absent.] Cartilage cells were seen mixed with the fibers of the distal third of the ligament, so that there was no sharp demarcation between the ligament and the underlying cartilage of the head.

The vessels in the vascular sheath of the ligamentum teres were either obliterated or greatly reduced in number. This is ascribed to the tension on the vessels and to pressure of the ligament against the margin of the acetabulum. There resulted a degeneration of the blood vessels of the head in the region of the fovea capitis femoris and a mucoid degeneration of the cartilage. In older chicks there was some attempt to repair the degenerative changes.

21. Storck, H.: Etiology and Early Diagnosis of Congenital Dislocation of the Hip, *Med. Klin.* 36:342-343 (March 29) 1940.

22. Whiston, G. C.: Histological Study of Growing Avian Femur (*Gallus Domesticus*) Following Experimental Dislocation of the Hip, *Anat. Rec.* 76:41-521 (April 25) 1940.

Dorsomedial flattening and ovoid distortion of the head together with coxa vara and anteversion of the neck were present. They are ascribed to abnormal tension of the ligamentum teres in the dislocated hip.

Abnormal stresses also produced definite changes in the internal structure, thickening of the cortex on the external convex side of the neck and shaft and thinning on the inner concave side, and thickening of the cortex of the trochanter major. This supports the contention of Koch and others that the internal structure of bone is determined in accordance with mechanical and mathematical laws to produce the greatest strength with a minimum amount of material. [ED. NOTE: This is a careful study of the secondary pathologic changes which occur in a dislocated hip. It does not deal with the primary pathologic conditions and causation of congenital dislocation and consequently cannot explain the entire picture of this lesion.]

Incidence.—Scaglietti²³ reviews and analyzes 15,272 cases of congenital dislocation of the hip. Of the patients, 83.46 per cent were females. In 57.13 per cent of the cases the dislocation was unilateral. Of these cases, the left hip was affected in 65.6 per cent. The condition occurred more frequently in northern than in southern Italy and more often in the plains than in the mountains.

Roentgen Examination and Diagnosis.—Burman and Clark²⁴ describe minutely the outlines and the markings evident in roentgenograms of infants between 26 days and 12 months of age. They illustrate Perkins' and Shenton's lines together with the lines that may be drawn to box the trochanters and add a line of their own which is drawn tangentially to the short ischiac arm (the iliac border of the Y cartilage of the acetabulum). The value of these lines in determining dislocation of the hip is demonstrated. Roentgen examination of the fetus in utero is shown to have little clinical value. They emphasize the value of diagnosing dislocation of the hip during the early months of life and state that this is fairly easily and accurately done by a proper coordination of clinical signs and roentgen readings. [ED. NOTE: This is a clear detailed exposition of this subject and worth careful study.]

Treatment.—West²⁵ lays down the following rules for treatment:

1. In children up to the age of 3 years closed reduction should be done and should be followed by immobilization in plaster for nine months.

23. Scaglietti, O.: *Modern Trends in the Treatment of Congenital Luxation of the Hip Joint*, Chir. d. org. di movimento **25**:308-320 (April) 1940.

24. Burman, M. S., and Clark, H. C.: *Roentgenologic Study of Hip Joint of Infant in First Twelve Months of Life, with Reference to Early Diagnosis of Its Congenital Dislocation*, Am. J. Roentgenol. **44**:37-47 (July) 1940.

25. West, E. F.: *Shelf Operation for Congenital Dislocation of the Hip*, M. J. Australia **1**:513-514 (April 13) 1940.

tions is then driven through the hole in the femur so that its inner end passes into the acetabulum just beneath the upper margin. He presents a few cases to demonstrate the efficacy of this procedure. [Ed. NOTE: One wonders what may be the eventual fate of this dead graft and what is to be done in advanced stages in which there is little or no acetabular rim persisting.]

Werner²⁹ cites 2 cases of spontaneous reduction of congenital dislocation of the hip, in which the reduction was proved to be spontaneous by roentgenograms taken before and after the reduction. The patient in the first case was a girl 1½ years of age with a frank dislocation of the left hip and a subluxation of the right. Treatment was advised but not carried out. Two years later all symptoms had disappeared, and the roentgenograms showed the hips were normal. In the second case, a roentgenogram made when the patient was 1 year of age showed a dislocation of one hip, and another made two years later showed a normal hip. No treatment had been given.

III. CONDITIONS INVOLVING GROWING AND ADULT BONE

Pituitary Dwarfism.—One of the functions attributed to the pituitary gland is the control of growth. In cases of pituitary inadequacy, particularly of inadequacy resulting from an infarction of this gland complicating infectious disease, there has been observed a type of dwarfism called the Levi-Lorain type.

Davidoff³⁰ indicates that the retardation of growth in this disease is likely to be of the infantile type, in which the bones are of light construction and there is generally a childlike build. This is usually associated with a retarded sexual development, but the patients are intellectually normal.

To stimulate growth in pituitary dwarfism Lurie³¹ has treated 20 children from 11 to 17 years of age with an extract containing the growth factor of the anterior lobe of the pituitary gland (prepared by Ayerst, McKenna and Harrison) and has obtained a growth in excess of the normal increment expected in children of similar ages.

Schaefer and Strickroot³² also report their experiences with an anterior pituitary extract containing the growth factor (antuitrin-G) in 18 cases. In 14 of the children there was a definite improvement in

29. Werner, R.: Spontaneous Healing of a Unilateral and a Bilateral Congenital Dislocation of the Hip, *Ztschr. f. Orthop.* **70**:326-332, 1940.

30. Davidoff, L. M.: Hyperpituitarism and Hypopituitarism, *Bull. New York Acad. Med.* **16**:227-243 (April) 1940.

31. Lurie, L. A.: Stimulation of Growth in Undersized Children by Means of Endocrine Therapy, *J. Med.* **21**:205-207 (July) 1940.

32. Schaefer, R. L., and Strickroot, F. L.: Endocrine Dwarfism, *Endocrinology* **26**:599-604 (April) 1940.

height. It is of interest to note that both of these investigators found it desirable to give these same children thyroid in doses as great as could be tolerated. Although it had been reported in some of these cases that doses of thyroid alone did not stimulate growth, there was demonstrated a synergism that made it desirable to give both glandular preparations to these patients.

The effects of dyspituitarism on the adult skeleton have been studied by Chester and Chester.³³ They made roentgen studies of patients who show the classic characteristics of acromegaly and report their observations on 8 patients. Five of these showed low dorsal kyphosis. The vertebrae of these patients showed an increase in the size of the bodies characterized by an accretion of bone on the anterior and lateral aspects. The height of the vertebral bodies remained the same. The disks, too, showed enlargement in the same directions as the bodies. This came about by abnormal growth of the perichondrium. At times the compression of the disks produced narrowing of the intervertebral space. These changes were more noticeable in the lower thoracic than in the lumbar portion of the spine. Osseous rims could frequently be found, but these rims differed from arthritic spurs in that the pituitary ridges were usually symmetric while the overgrowths attributable to arthritis were irregular spiculations.

The Thyroid Gland and the Skeletal System.—The effects of hypothyroidism have been observed in cretins and have been subjected to careful study. By means of the administration of thyroid it has been possible to learn the role played by the thyroid gland on the skeletal system. Wilkins³⁴ has compared the rate of osseous development and of mental development of patients with hypothyroidism with that of normal children. He states that by administering subtoxic doses of desiccated thyroid he is able to produce a growth curve that parallels, and at times is better than, that of the normal growth curve.

Kerley³⁵ reports the cases of 2 patients with congenital myxedema who under subtoxic thyroid therapy have grown up with normal physical and intellectual qualities.

33. Chester, W., and Chester, E. M.: Vertebral Column in Acromegaly, *Am. J. Roentgenol.* **44**:552-557 (Oct.) 1940.

34. Wilkins, L.: The Rates of Growth, Osseous Development, and Mental Development in Cretins as a Guide to Thyroid Treatment, *J. Pediat.* **12**:429-438 (April) 1938; *The Pharmacopoeia and the Physician: Thyroid Medication During Childhood*, *J. A. M. A.* **114**:2382-2387 (June 15) 1940; Recent Studies on the Diagnosis of Hypothyroidism in Children, *Pennsylvania M. J.* **44**:429-432 (Jan.) 1941.

35. Kerley, C. G.: End Results in the Cretin, *Arch. Pediat.* **57**:432-436 (July) 1940.

The studies of Wilkins³⁶ are of particular interest in their clarification of epiphyseal changes that have hitherto not been generally understood. There is present in patients with hypothyroidism an abnormality of the centers of ossification that simulates the changes of Legg-Perthes disease. These conditions are, however, distinct entities. Ossification of the normal epiphysis develops from a single focus in the center of the epiphyseal cartilage. In hypothyroidism, however, there are multiple irregular foci scattered through the epiphyseal plate. As these enlarge and coalesce there is presented a roentgen picture of stippling or fragmentation. This condition, named by Wilkins epiphyseal dysgenesis, responds favorably to thyroid therapy. Epiphyses that have been retarded in their ossification because of the hypothyroid condition may show the dysgenetic changes even after therapy has been started, but ultimately the coalescence of the multiple centers leads to a normal-looking epiphyseal calcification.

There is, however, a type of stippling that is not attributable to thyroid dysfunction. This condition, the epiphyseal dysplasia punctularis, is apparently a distinct entity of unknown origin.³⁷

Parathyroid Glands and Bony Changes.—The relation that exists between the parathyroid glands and changes in bone has been well established. The recent literature³⁸ contains many reports that bear out the present concepts. Coordination of the various manifestations of hyperparathyroidism is accomplished by Kyser,³⁹ Bowers⁴⁰ and Rynearson.⁴¹

An excellent study is presented by Jaffe.⁴² In addition to a presentation of the theoretic concepts and the clinical picture he makes

36. Wilkins, L.: Epiphyseal Dysgenesis Associated with Hypothyroidism, *Am. J. Dis. Child.* **61**:13-34 (Jan.) 1941.

37. McCullough, J. A. L., and Sutherland, C. G.: Epiphyseal Dysplasia Punctularis (Stippled Epiphyses): Report of Case Not Associated with Hypothyroidism, *Radiology* **34**:131-135 (Feb.) 1940.

38. Hart, D., and Gardner, C. E., Jr.: Hyperparathyroidism: Report of Nine Cases, *South. Surgeon* **9**:41-58 (Jan.) 1940. Baumgartner, C. J.: Hyperparathyroidism—Normal Chemistry—Rapid Recalcification Following Removal of Large Parathyroid Adenoma, *West. J. Surg.* **48**:324-327 (May) 1940. Heller, E. P.: Hyperparathyroid Disease and Manifestations of Interest to Industry, *Indust. Med.* **9**:125-135 (March) 1940.

39. Kyser, F. A.: Hyperparathyroidism, *Proc. Staff Meet., Mayo Clin.* **15**:179-181 (March 20) 1940.

40. Bowers, R. F.: Hyperparathyroidism, *Internat. Clin.* **3**:277-285 (Sept.) 1940.

41. Rynearson, E. H.: Hyperparathyroidism, *M. Clin. North America* **21**:1033 (July) 1940.

42. Jaffe, H. L.: Hyperparathyroidism, *Bull. New York Acad. Med.* **16**:311 (May) 1940.

a careful survey of the pathologic changes in the skeleton. He indicates that the bony changes observed, even in patients with moderate bony porosity, are characterized by the perforation of the bony trabeculae by connective tissue tracts. Osteoclastic action is noted with little evidence of new bone formation. Instead, the connective tissue forms islands in the decalcified areas, and as the disease progresses there is an enlargement of these islands so that the connective tissue masses ultimately merge to make large fibrous scars. Though these fibrous scars are distributed generally, they are likely to be present with greater frequency in the bones that are subjected to the largest amount of functional stress, such as the long tubular bones, the vertebral column and the terminal phalanges of the fingers (clubbed fingers). He explains the development of the brown tumor on the basis of formation of such a decalcified area with subsequent cystic degeneration produced by ischemia or hemorrhage. He emphasizes the importance of not confusing the solitary giant cell tumor with the brown tumor and takes up in detail the differential diagnosis of this condition as well as of other confusing diseases.

A rather interesting study is reported by Helfet.⁴³ Working on the theory that parathyroid dysfunction produces changes in the phosphorus rather than in the calcium of the skeleton, he has been prescribing aluminum acetate in the belief that the aluminum will combine with the phosphate in the intestine to form aluminum phosphate. This product is then excreted by the bowel. He offers several case reports to show that under such therapy the patients improved. The astringency of the drug has made it necessary to administer the medication in small doses, but he has found slow but definite improvement in the condition of his patients. He also links rheumatoid arthritis with hyperparathyroidism and therefore administers aluminum acetate to rheumatic persons. In these patients, too, he has found a definite improvement. [ED. NOTE: The evidence against this "new conception" is so strong that more adequate substantiation of the author's thesis is desirable.]

At this point attention should also be called to polyostotic fibrous dysplasia, a condition which is often mistaken for a manifestation of hyperparathyroidism or for the so-called solitary bone cyst. Although the patient of Moehlig and Schreiber⁴⁴ showed abnormalities that were attributable to dyspituitarism, they felt convinced that the bony changes

43. Helfet, A. J.: New Conception of Parathyroid Function and Its Clinical Application: Preliminary Report on Results of Treatment of Generalized Fibrocystic and Allied Bone Diseases and of Rheumatoid Arthritis by Aluminum Acetate, *Brit. J. Surg.* **27**:651-677 (April) 1940.

44. Moehlig, R. C., and Schreiber, F.: Polyostotic Fibrous Dysplasia: Report of Case with Unilateral Involvement, *Am. J. Roentgenol.* **44**:17-23 (July) 1940.

represented a skeletal developmental anomaly. Adams and associates⁴⁵ report 10 similar cases and found that these changes appear early in childhood after monomelic tendencies and are usually called to the attention of the physician because of pain, fractures and malunion. Since the causation of this condition is not clear and since the cystic changes cannot be eradicated by operation, they recommend limiting treatment to procedures giving symptomatic relief and preserving normal function.

Growth Deficiency from Hypogonadism.—Growth deficiencies can also result from hypogonadism. Under treatment with testosterone propionate⁴⁶ a 15½ year old eunuch showed a spurt in growth that brought him to a much more normal height. The ratio of the length of the long bones to the length of the short bones likewise became far more normal than before treatment. Chorionic gonadotropin⁴⁷ administered for sexual underdevelopment was also found to be an excellent stimulant to bone growth. Observations on the effects of such treatment on 21 patients with genital dystrophy showed considerable improvement in the rate of skeletal development. The value of treatment with chorionic gonadotropin is most apparent in children under 13 years of age, while its administration to children under 5 years requires great caution. In general, it was noted that the taller boys have relatively moderate rises in the growth curve, while the more stunted patients have much more marked spurts in growth. There is also a concomitant acceleration in osseous development of the carpal bones as indicated by roentgenograms. There is, on the other hand, no evidence of premature closure of the epiphyses. It is possible that the increase in height may be produced by the stimulation of the gonads, which in turn stimulate the growth factor in the anterior pituitary lobe. In one report⁴⁸ it is suggested that hypogonadal skeletal changes are characterized by thinning of the cortical layer and of the bony trabeculae, by roughening of the metaphysial margin of the growing bone and by an associated tendency to dental caries.

Brittle Bones.—The possibility that bone fragility of the type associated with blue scleras, usually attributed to a hereditary mesenchymal

45. Adams, C. O.; Compere, E. L., and Jerome, J.: Regional Fibrocystic Disease, Surg., Gynec. & Obst. **71**:22-32 (July) 1940.

46. Rapfogel, I.: Effect of Testosterone Propionate upon Skeletal Development of a Eunuch, Endocrinology **27**:179-184 (Aug.) 1940.

47. Dorff, G. B.: Chorionic Gonadotropic Effects on Height and Osseous Development in Sexually Underdeveloped Young Boys, Endocrinology **27**:403-411 (Sept.) 1940; Chorionic Gonadotropic Effects on Growth of Sexually Underdeveloped Older Boys, Am. J. Dis. Child. **60**:1043-1057 (Nov.) 1940.

48. Hurxthal, L. M., and Hare, H. F.: Bone Changes in Primary Hypogonadism, Lahey Clin. Bull. **1**:9-12 (April) 1940.

hypoplasia, is etiologically related to Paget's disease is suggested by the case of Nichols.⁴⁹ The presence of otosclerosis as part of the syndrome is indicated by Fox and Sweet,⁵⁰ in whose cases there is evidence that development of deafness takes place in patients who pass their twentieth birthday.

In this connection it is interesting to note Funk's⁵¹ opinion that there has been confusion in the literature about fragilitas ossium. He differentiates Lobstein's osteopsathyrosis from Vrolik's osteogenesis imperfecta. The latter is characterized by deformities of growth, occurrence of fractures in utero and early death, usually before the child becomes 4 years old. The blue scleras constitute, in his opinion, an unreliable sign. In the Lobstein type, there are no disturbances of growth. The fractures usually begin after 2 years of age, and the patient may live a normal span of life. Although he considers the condition a hereditary constitutional anomaly, he questions the relation to parathyroid malfunction and points out that treatment with thymus extract, estrogens, androgens and adrenal, thyroid and pituitary extracts has failed to give relief. In his own case, a diet high in calcium and phosphorus with vitamin D failed to produce improvement.

Osteopetrosis.—The peculiar osteodystrophic disease, osteopetrosis, described by Albers-Schönberg has received some attention. Its existence without the production of any symptoms is emphasized by Howard and Gonzalez,⁵² who accidentally found marblé bones in a young woman who was being given a roentgen examination for a possible foreign body. In another case report⁵³ autopsy studies of a 1 year old baby indicated that compensatory myeloid changes may occur in the lymph nodes, spleen and liver. In this patient, too, periosteal reaction was observed in conjunction with the sclerotic changes in the bones. The production of generalized osteosclerosis by an exogenous factor is called to one's attention by several observers. Wilkie⁵⁴ reports 2 cases of

49. Nichols, B. H.: *Fragilitas Ossium: Brittle Bones and Blue Sclerae; Hereditary Mesenchyme Hypoplasia*, Cleveland Clin. Quart. **7**:58-65 (Jan.) 1940.

50. Fox, M. S., and Sweet, S. J.: *Brittle Bones Associated with Deafness and Blue Scleras: Report of Syndrome in Two Persons of One Family*, Arch. Otolaryng. **32**:506-511 (Sept.) 1940.

51. Funk, P.: *Lobstein's Osteopsathyrosis: Syndrome of Abnormal Fragility of Bones with Blue Sclera and Tympanic Membrane*, Schweiz. med. Wchnschr. **70**:473-479 (June 1) 1940.

52. Howard, C., and Gonzalez, J.: *Osteopetrosis: Report of a Case*, Bull. New York M. Coll., Flower & Fifth Ave. Hosps. **3**:165-171 (Oct.) 1940.

53. Beatty, S. R., and Ritchie, G.: *Osteopetrosis: Case Report*, Radiology **34**:338-342 (March) 1940.

54. Wilkie, J.: *Two Cases of Fluorine Osteosclerosis*, Brit. J. Radiol. **13**:213-217 (June) 1940.

osteosclerosis caused by exposure to fluorine compounds. Two other communications indicate that osteosclerosis can be produced by drinking water that contains an excessive amount of fluorine. Apparently these patients usually show mottled tooth enamel and hardening of the bones that may vary in degree from thickening of the vertebrae to complete osteopetrosis. In Madras, India, where the disease was endemic on account of the high fluorine content of the water, the disease was frequently ushered in by rheumatic pains, chiefly in the back, shoulders and hips, and often showed pathologic changes in the ligaments, which lost their elasticity and became ossified. The differences shown by the various groups of cases reported lead one to believe that osteopetrosis is a manifestation of several conditions which may be etiologically and pathologically independent.

Osteoporosis.—Senile osteoporosis is no longer being dismissed with the comment that "it is the bone atrophy of old age." Black⁵⁵ studied 208 cases of vertebral osteoporosis. He found that women are much more subject to this condition than men, a ratio of 4 to 1. His patients were all over 45, averaging 62 years of age. The clinical pictures presented varied considerably. Some patients had no symptoms referable to this. Others, however, had aching in the lower part of the back with weakness and fatigue. This discomfort could be precipitated by light strain into an acute backache with sharp radiations of pain. Most of the patients showed a flattening of the normal lumbar curve with a marked increase in the thoracic kyphosis and an exaggerated cervical lordosis. Occasionally movements were found to be considerably restricted. Roentgen examinations showed pronounced atrophy of the vertebrae, with development of biconcave bodies and expanded intervertebral disks. In the treatment, dietary supervision was undertaken to assure the proper ratio of carbohydrate, fats, proteins and vitamins, with additional large amounts of calcium and phosphorus. No definite improvement could be attributed to diet alone. Relief, however, could be obtained by supporting the back and applying local physical therapy.

An interesting chemical analysis of bone in a 10 year old child is presented by Hansen, Palmer and Nelson.⁵⁶ This child had extensive carcinoma of the liver and showed thinning of the bones early in the disease. A specimen of bone showed a marked replacement of bone

55. Black, J. R.: Senile Osteoporosis of Spine, *Proc. Staff Meet., Mayo Clin.* 15:619-623 (Sept. 25) 1940.

56. Hansen, A. E.; Palmer, L. S., and Nelson, J. W.: Composition of Bone in Extreme Osteoporosis Associated with Hepatoma, *Proc. Soc. Exper. Biol. Med.* 43:206-207 (Jan.) 1940.

by water and lipids and about one third less than normal of calcium, phosphorus, magnesium and carbon dioxide.

Brown and Ginsburg⁵⁷ present the case of a patient with bone atrophy and metastatic calcification associated with severe glomerulonephritis. They feel that the skeletal demineralization may have resulted from prolonged acidosis with increased thyroid activity.

Chondroplasias.—Judging from the large number of reports on epiphyseal dysplasias, there is a growing interest in such diseases as achondroplasia and dyschondroplasia (Ollier's disease). Archeologically,⁵⁸ achondroplasia has been traced practically to the neolithic era. In Egypt, a humerus showing signs of this anomaly was found in the tomb of King Zer of the First Dynasty; a complete achondroplastic skeleton has been found that has been assigned to the predynastic period, the Badarian era. Therefore, this is one of the oldest diseases known.

Usually achondroplasia does not become apparent until years after birth. Thalheimer and Gershon-Cohen,⁵⁹ however, indicate that it is possible to diagnose such a condition prenatally. They refer to Cronberg, who reported a case of achondroplasia recognized before birth by means of roentgen examination. In their own case the condition was not diagnosed till six months after delivery, but by referring to the prenatal roentgenograms they were able to see changes that could have warranted the diagnosis before birth. The changes observed were lumbar kyphosis, irregularity of the lumbar vertebral bodies, widened and deformed costochondral junctions and short and wide bony shafts that were flared at the ends.

Diagnosis of the chondroplasias in growing children and in adults is not without difficulties. Partly this may be attributed to the profusion of names for the manifestations, names used interchangeably by some authors.⁶⁰ The differential diagnosis is made difficult by the similarity of the specimens to those of cartilaginous tumors. Carter⁶¹ reports a case in which roentgenograms, photographs and specimens suggest a neoplasm, but both he and Phemister classify the case as one of Ollier's

57. Brown, C. L., and Ginsburg, I. W.: Osteoporosis Associated with Extensive Metastatic Calcification and Chronic Renal Disease, *Arch. Path.* **30**:108-121 (July) 1940.

58. Bleyer, A.: Antiquity of Achondroplasia, *Ann. M. Hist.* **2**:306-307 (July) 1940.

59. Thalheimer, E. J., and Gershon-Cohen, J.: Chondrodystrophy: Prenatal Diagnosis Possible, *Radiology* **35**:495-496 (Oct.) 1940.

60. Zimmermann, C. A. W.: Hereditary Deforming Chondrodysplasia, *J. Missouri M. A.* **37**:294-298 (July) 1940.

61. Carter, R. M.; Ollier's Dyschondroplasia: Report of Case, *J. Bone & Joint Surg.* **22**:1063-1069 (Oct.) 1940.

dyschondroplasia. The condition is further complicated by the possibility of neoplastic changes in a true hereditary or congenital deformity. Gillespie and Siegling⁶² call attention to the confusion of Morquio's disease (osteochondrodystrophia deformans) with dysostosis multiplex. The latter disease is characterized by dwarfed stature, scaphocephalic and chondrodystrophic deformities of the skull, shortness of the neck and trunk, abdominal protrusion, kyphosis of the spine, partial ankylosis of the joints and clouding of the cornea. It is emphasized that though Morquio's disease is familial and usually associated with normal mentality, dysostosis multiplex is congenital, shows a retarded mentality and usually is accompanied by the nonskeletal symptom clouding of the cornea. The hereditary character of the disease is stressed by Mörch.⁶³ Jacobson⁶⁴ explains the structure of epiphysis-like exostoses on the basis of a mutual polarity that exists wherever cartilage and bone are growing together. Butler and Debenham⁶⁵ demonstrate that secondary disease can result from the bony masses; they report a case in which there was a false saccular aneurysm produced by pressure and erosion on the femoral artery. Abell⁶⁶ reports a patient with 91 tumors.

Paget's Disease.—The writings on osteitis deformans consist chiefly of reports of cases. Though there has been no great progress in the understanding of the causes or treatment of this disease, it becomes clear that the condition is not rare. Sugarbaker⁶⁷ reports 51 cases from the Henry Ford Hospital. The patients were all above 40 years of age. The bones most frequently involved were the skull, the spine, the pelvis, the femur and the tibia. Involvement of a single bone was present in 24 per cent of the patients. The pain of these patients could be attributed to the tension on the periosteum and ligaments. The chemical studies revealed normal blood calcium and phosphorus, but the phosphatase readings showed an increase that varied with the extent of osseous involvement (average, 12.74 Bodansky units). Fractures may complicate the course of the disease (15 per cent), and sar-

62. Gillespie, J. B., and Siegling, J. A.: Dysostosis Multiplex, *J. Bone & Joint Surg.* **22**:171-175 (Jan.) 1940.

63. Mörch, E. T.: Achondroplasia Is Always Hereditary and Is Inherited Dominantly, *J. Hered.* **31**:439-444 (Oct.) 1940.

64. Jacobson, S. A.: Contribution to Pathogenesis of Multiple Hereditary Osteochondromatosis: Experimental Study, *Am. J. Cancer* **39**:220-223 (June) 1941.

65. Butler, E., and Debenham, M. W.: Traumatic False Saccular Aneurysm Resulting from Erosion of Femoral Artery in Patient with Hereditary Dyschondrodysplasia, *West. J. Surg.* **48**:511-513 (Aug.) 1940.

66. Abell, I.: Chondrodysplasia—Report of a Case, *Arch. Surg.* **41**:217-221 (Aug.) 1940.

67. Sugarbaker, E. D.: Osteitis Deformans (Paget's Disease of Bone). Review of Fifty-One Cases, *Am. J. Surg.* **48**:414-421 (May) 1940.

comatous degeneration occurs sufficiently often to make one be on the alert for the condition, especially after the disease has been present for ten or fifteen years.

Attempts to attribute this disease to disturbances of the endocrine system have not been convincing. Rose⁶⁸ reports 3 cases, in 2 of which there was concomitant diabetes mellitus. Nichols⁶⁹ calls attention to the resemblance of the bony changes in Paget's disease to those in hyperparathyroidism but stresses that each of these diseases has definite diagnostic features and that they should not be confused. The possibility of mistaking the headache of Paget's disease for that of pituitary neoplasm is presented by Pond,⁷⁰ and differential diagnosis of the two is given. The therapy for osteitis deformans is still unsatisfactory, though there have been encouraging results reported from the use of extracts of adrenal cortex.

Xanthomatosis.—Hertzog, Anderson and Beebe⁷¹ performed an autopsy on a patient who had died from a fatal aplastic anemia and observed changes in the fat storage which suggested Hand-Schüller-Christian disease. Although there were no gross bony changes to be found clinically, the bone marrow in the shaft of the femur was red and hypoplastic on microscopic examination. Jelsma⁷² reported 3 cases with typical cranial defects in which roentgen therapy produced a 60 per cent improvement.

Rickets.—Assuming that rickets develop in the premature infant unless adequate preventive measures are taken, Zelson⁷³ studied the effects of single massive doses of vitamin D in 46 premature infants. In most of his cases 600,000 U. S. P. units in the form of vitamin D₂ (calciferol) or D₃ (activated 7-dehydrocholesterol) was administered parenterally. Rickets did not develop in any of the patients so treated.

Vollmer⁷⁴ discusses the question of the toxicity of large doses of vitamin D. He indicates that in the irradiated ergosterols there are present many by-products which may prove toxic. If, however, one can

68. Rose, M. E.: Paget's Disease, Illinois M. J. 77:232-234 (March) 1940.

69. Nichols, D. R.: Osteitis Deformans (Paget's Disease of Bone): Report of Case, Proc. Staff Meet., Mayo Clin. 15:182-184 (March 20) 1940.

70. Pond, C. W.: Paget's Disease, Pituitary Tumor and Abscess of Sphenoid Sinus: Report of Case, Ann. Otol., Rhin. & Laryng. 49:500-509 (June) 1940.

71. Hertzog, A. J.; Anderson, F. G., and Beebe, G. W.: Reticulo-Endotheliosis with Lipoid Storage, Arch. Path. 29:120-124 (Jan.) 1940.

72. Jelsma, F.: Xanthomatosis: Report of Three Cases, South. M. J. 33: 1256-1260 (Dec.) 1940.

73. Zelson, C.: Prevention of Rickets in Premature Infants with Parenteral Administration of Single Massive Doses of Vitamin D, J. Pediat. 17:73-78 (July) 1940.

74. Vollmer: Treatment of Rickets and Tetany by Parenteral Administration of One Massive Dose of Vitamin D, J. Pediat. 16:419-432 (April) 1940.

administer calciferol or activated 7-dehydrocholesterol alone, the toxic dose is many times greater than the one necessary for treatment. On the basis of results obtained in 158 children he advocates the use of a single massive dose, usually 600,000 U. S. P. units of vitamin D. No toxic manifestation appeared in any of the children so treated.

The method of giving vitamin D preparations also comes up for discussion. Vollmer prefers the parenteral route. Because administration of the usual oily solution is an uncomfortable procedure and because there is an appreciable delay in the utilization of the vitamin so administered, he suggests adding ether to the oily mixture. This technic has resulted in much more rapid utilization of the effective agent; according to his experience the serum calcium and phosphorus can become normal within three to seven days and calcification can be shown roentgenographically within a week. Complete recalcification was usually found at the end of a month.

Albright and others⁷⁵ report an interesting case of rickets associated with dwarfism and nephrocalcinosis. The patient, a girl 13 years old, showed normal serum calcium and low serum phosphorus and high serum phosphatase, clearly demonstrating the rachitic nature of her disease. She had massive calcareous deposits in the kidneys, hyperchloremia and a low level of serum carbonates. In addition to this, she showed a marked retardation in growth. The authors interpret the clinical picture in the following way: There was an inability to produce ammonia together with a failure to excrete acid urine as a result of renal disease. Furthermore, there was an inadequate amount of base with which to excrete the mineral acid. The calcium substituted for the base and was lost through urinary excretion, producing a low level of serum calcium. This stimulated secondary parathyroidism, with resultant hypophosphatemia and low phosphorus rickets. When the patient was given a low sodium chloride diet reenforced with vitamin D and sodium citrate and citric acid, there was definite improvement in her condition. Albright does not consider this a case of renal rickets but prefers to call it one of nephrocalcinosis with rickets and dwarfism.

Scurvy.—There have been many clinical reports of patients suffering from scurvy as a result of dietary deficiencies. There has also been a considerable amount of experimental work on animals in which scurvy was produced. Crandon, Lund and Dill,⁷⁶ however, have experimentally produced scurvy in an adult human being and have carefully studied the manifestations. A man was placed on a vitamin C-free diet

75. Albright, F., and others: Metabolic Studies and Therapy in Case of Nephro-Calcinosis with Rickets and Dwarfism, *Bull. Johns Hopkins Hosp.* 65:7 (Jan.) 1940.

76. Crandon, J. H.; Lund, C. C., and Dill, D. B.: Experimental Human Scurvy, *New England J. Med.* 223:353-369 (Sept. 5) 1940.

that was kept supplemented with all other known vitamins. This regimen was maintained for a period of six months. The earliest clinical manifestations did not appear until one hundred and thirty-two days of adherence to this diet had elapsed. The tests for scurvy generally used did not prove to be sensitive indexes in the early stages of the disease. Thus, the plasma ascorbic acid level was zero for thirteen weeks before the first evidence of clinical disease was noted. The vitamin level in the white cell-platelet layer of the centrifuged blood, however, proved to be a good index of the patient's status with regard to vitamin C. The first definite clinical sign consisted of hyperkeratotic papules containing ingrowing hairs. Failure of wound healing was an important finding, the tissues showing a lack of intercellular substance. There was no evidence of lowered resistance to infection in the scorbutic state. The scurvy responded rapidly to intravenous injection of ascorbic acid.

Caisson Disease.—Caisson disease is caused by too rapid decompression after tissues have become saturated with nitrogen gas. During compression the pulmonary air is saturated with nitrogen under pressure. The nitrogen is carried to the tissues, whereupon the entire body becomes saturated. Fat takes up five times more nitrogen than other tissues. Complete saturation with nitrogen requires about one hour, but this time is shortened by exercise. During the decompression the reverse process takes place. The saturated tissues give off nitrogen to the blood, which becomes desaturated in the lungs until atmospheric pressure is reached. If decompression is too rapid, bubbles of nitrogen form in the body and cause embolism. Emboli so formed are most common in venous blood, fatty tissues, synovial fluid and structures of the nervous system.

Coley and Moore⁷⁷ tabulate systematically the symptoms of caisson disease as follows: (1) cerebrospinal—numbness, tingling, coma, collapse, Ménière's syndrome; (2) cardiovascular—signs of embolism; (3) pulmonary—dyspnea; (4) visceral—nausea and vomiting; (5) dermal—pruritus; (6) skeletal—pain present in 85 to 90 per cent of cases.

The long bones are the favored sites; the vertebrae and the membranous bones escape, perhaps because of the high proportion of red marrow as compared with fatty marrow. The lower extremities are affected more often than the upper. The pain is due to gas being confined in an unyielding space.

The pathologic change which accompanies caisson disease is caused by nutritional disturbance as a result of embolism or pressure on a blood vessel from without or both. The result is aseptic necrosis which

77. Coley, B. L., and Moore, M., Jr.: Caisson Disease with Special Reference to Bones and Joints: Report of Two Cases. *Ann. Surg.* **111**:1065-1075 (June) 1940.

is followed by attempts at repair by osteoclasia, creeping substitution and eventual delimitation by calcification.

The lesions are distinguished roentgenographically by their multiple distribution in medullary bone. The osseous shaft is not expanded, and the infarction presents a region of irregularly increased density surrounded by a region of calcification on the outside of which is normal bone. According to Walker,⁷⁸ this region is necrotic bone with empty lacunar spaces walled off by a thin rim of calcium. The articular changes resemble roentgenographically those of arthritis deformans.

Rendich and Harrington⁷⁹ sum up the chronic osseous changes of caisson disease as follows: (1) aseptic necrosis of hips, shoulders or knees; (2) medullary calcification in diaphysial ends of long bones; (3) hypertrophic arthritis, (4) aseptic necrosis with osteoarthritis as well as medullary calcification.

Coley and Moore⁷⁷ express the belief that the characteristic lesions of the bones can result from one insult of sufficient severity and that caisson disease may be the cause of vague pains in the bones and joints caused by regions of aseptic necrosis which may later be discovered. They stress the importance of the clinical picture in the field of compensation claims.

Gordon and Heacock⁸⁰ present a case in which the presence of air in the synovial space was demonstrated roentgenographically. To their knowledge this is the first case on record in which the clinical diagnosis was supported roentgenographically.

IV. TUBERCULOSIS OF BONES AND JOINTS

General Considerations.—Meyer and Froyez-Roederer⁸¹ report their studies at the Franco-American Foundation of Berck-Plage to determine the frequency of infection by the bovine tubercle bacillus. Pus obtained by puncture or more rarely from fistulas in 239 cases of osteoarticular tuberculosis and in 23 cases of tuberculosis of the cervical lymph nodes was studied by culture and, when necessary, by animal inoculation. Of the 250 strains of tubercle bacilli isolated, 242 were the human type and 8 the bovine type. There were 5 bovine infections in 235 cases of osteoarticular tuberculosis and 3 bovine infections in 12 cases of tuberculosis of the cervical lymph nodes.

78. Walker, W. A.: Aseptic Necrosis of Bone Occurring in Caisson Disease: Case Report, *J. Bone & Joint Surg.* **22**:1080-1084 (Oct.) 1940.

79. Rendich, R. A., and Harrington, L. A.: Roentgen Findings in Caisson Disease of Bone, with Case Reports, *Radiology* **35**:439-448 (Oct.) 1940.

80. Gordon, J. O., and Heacock, C. H.: Roentgenologic Demonstration of Localized Gas in Caisson Disease, *J. A. M. A.* **114**:570-571 (Feb. 17) 1940.

81. Meyer, K., and Froyez-Roederer: The Frequency of Infection with Bovine Bacilli in Osteo-Articular and Cervical Lymph Node Tuberculosis, *Ann. Inst. Pasteur* **64**:167-172 (Feb.) 1940.

Combining their observations with those of other investigators in France, they obtained 7 cases of bovine bacillus infection in 445 cases of tuberculosis of the cervical lymph nodes. They conclude that the bovine tubercle bacillus plays an unimportant part in causing the disease in France. This is considered due to the infrequent consumption of raw milk.

In postulating the role of the pleural lymphatics in the pathogenesis of cold abscesses of the wall of the chest and paravertebral abscesses, Burke⁸² says that particulate matter (a mixture of colloidal thorium dioxide and finely divided lampblack and tubercle bacilli in suspension in isotonic solution of sodium chloride) injected into the pleural spaces of guinea pigs is, in part at least, transported to the parasternal and the para-aortic lymph nodes. Observations on human subjects who have come to necropsy indicate that in man tubercle bacilli and particulate matter, such as silicious material, are conveyed from the pleural spaces to the parasternal and para-aortic lymph nodes. This evidence provides a probable explanation of the formation of cold abscesses of the anterior wall of the chest, and makes it seem probable that the transfer of tubercle bacilli from the pleural spaces to the para-aortic lymph nodes may in certain instances play a part in the evolution of paravertebral abscesses. [ED. NOTE: In our experience paravertebral abscesses and abscesses of the anterior wall of the chest unassociated with foci in the vertebrae, the ribs or the sternum are rare.]

Law⁸³ gives the history of a case which he states was one of multiple cystic tuberculosis of bones. The patient was a 6 year old girl with tuberculosis of the dorsal portion of the spine and pulmonary tuberculosis. While she was under treatment for this condition by spinal fusion and rest, multiple cystic lesions of the Jüngling type and entirely asymptomatic were found involving 22 bones; none of the lesions were in the small bones of the hands and feet. Serial roentgenograms were taken of all lesions. Healing of every lesion was shown to take place spontaneously, anywhere from five and a half to forty-eight months after the patient came under observation. The roentgen observations of diagnostic value are discussed. These include round, smooth or irregular punched-out areas of decreased density, with a thin cortex and little or no surrounding sclerosis and without periosteal involvement, expansion or abscess formation.

82. Burke, H. E.: Role of Pleural Lymphatics in Pathogenesis of Cold Abscesses of Chest Wall and Paravertebral Abscesses, *J. Thoracic Surg.* **9**:506-519 (June) 1940.

83. Law, J. L.: Multiple Cystic Tuberculosis of Bones: Its Roentgen Picture and Reparative Process as Seen in Serial Roentgenograms, *Radiology* **35**:328-335 (Sept.) 1940.

Ellis⁸⁴ calls attention to the evidence that Jüngling's disease is osteal sarcoid and not cystic tuberculosis of the bones, as it is considered by many American authors. Cases of this disease have the following characteristics: There is lack of necrosis in the lesions; sinuses do not form; usually the patient does not react to old tuberculin; the lesions are solid and appear to be cystic only in the roentgenogram.

Because of the rarity of tuberculosis of shafts of the long bones in the United States, as revealed by an intensive search of the literature, Carrell and Childress⁸⁵ sent a questionnaire to 250 leading orthopedic surgeons in the United States and collected a series of 95 cases.

In every case in this group the condition had been definitely proved to be tuberculous by microscopic section and animal inoculation, or by the latter method alone. Only lesions of shafts (diaphyses and metaphyses without involvement of the joints) of long bones were accepted. Whether a lesion was in the diaphysis or the metaphysis is not recorded. In 95 patients, 123 long bones of the extremities were affected. Seven patients had involvement of 2 bones; 4, of 3 bones; 2, of 4 bones; and 1, of 7 bones. The tibia was involved in 36 patients (29 per cent), and the femur was affected in 33 (27 per cent). This marked frequency of occurrence in these 2 bones was present uniformly, regardless of the age group.

Contrary to current opinion, shaft tuberculosis does not occur predominantly in childhood. Of this series of 95 patients, 46 (48 per cent) were 20 years of age or more at the time of onset. Associated active tuberculous lesions were present in 37 patients. Of the total series of 95 patients, only 11 had involvement of the joints.

Eighteen deaths occurred in 95 patients. Seventeen of these deaths were in patients with allied lesions, and 14 deaths were in patients with a duration of symptoms of one year or less.

The end results were known in 71 of the 95 cases. Healing occurred in 92 per cent of 13 patients treated by curettage or saucerization and closure. In 3 cases bone chips were packed into the osseous cavity after curettage. The addition of chips may aid in a more rapid repair of the defect. Of the 38 cases in which treatment was by incision and drainage, healing took place in 25 (66 per cent); there was no improvement in 6, and death occurred in 7. In many of these cases, in which there were draining sinuses, conditions were not suitable for closure, and in others, no doubt, there had first been surgical treatment after a diagnosis of pyogenic osteomyelitis.

84. Ellis, F. A.: Jüngling's "Osteitis Tuberculosa Multiplex Cystoides" Is Not Cystic Tuberculous Osteitis, *Acta med. Scandinav.* **104**:221-224, 1940.

85. Carrell, W. B., and Childress, H. M.: Tuberculosis of Large Long Bones of Extremities, *J. Bone & Joint Surg.* **22**:569-588 (July) 1940.

There were only 5 instances of spontaneous healing. The facts that 37 patients had had symptoms for over one year and that 19 had had complaints for over two years before being treated demonstrate the fallacy of the inference that healing might eventually have taken place in more patients if surgical intervention had been delayed.

[ED. NOTE: Tuberculosis of diaphyses of long bones is rare, but lesions of metaphyses without involvement of the joints are more common. Although the number of patients so treated is not large, it would appear that curettage or excision of the lesion and closure of the wound give the best results.]

Operative Treatment of Tuberculosis of Bones and Joints.—Bosworth⁸⁶ writes of various aspects of the treatment of tuberculosis of bones and joints. This is based on experience with a large number of cases in a New York municipal hospital devoted to the care of tuberculous patients. He stresses the importance of the patient's general health, the discovery of concomitant diseases, good nursing care, occupational therapy, education and other measures to improve the morale. In addition to this he is convinced of the value of arthrodesis. He believes that it is necessary to establish the diagnosis by biopsy but warns of the importance of performing the arthrodesis at once or soon after the exploratory operation to avoid the breaking down of the wound or the formation of sinuses. He describes the operations which he has found most useful in the treatment of various joints as follows:

Spinal Fusion: The Hibbs technic is followed in its essentials. Subperiosteal exposure of the laminae and thorough removal of the attached ligaments are emphasized, as well as removal of as much cartilage as possible from the articulations. Except in the cervical region, where fusion readily takes place, strip grafts from the ilium are used to augment the fusion prepared by chips turned up and down from the laminae or cut from the spinous processes. If the patient's condition is not good, fusion is performed on only one side of the area (hemifusion). The other side is operated on two or four weeks later. If the area to be fused is long, four hemifusions are usually performed.

Sacroiliac Fusion: A truncated block of sacrum, sacroiliac joint and ilium is removed from the posterolateral portion of the ilium. After the sacral bone and joint cartilage are removed, the iliac portion of the block is countersunk across the line of the joint.

86. Bosworth, D.: Tuberculosis of Osseous System: Tuberculosis Involving Skeleton Other Than Spine, *Quart. Bull., Sca View Hosp.* 5:189-220 (Jan.) 1940; Tuberculosis of Osseous System: Complicating Factors in Management of Osseous or Arthrogenic Tuberculosis, *ibid.* 5:320-340 (April) 1940; Tuberculosis of Osseous System: Operative Methods, *ibid.* 5:441-470 (July) 1940.

Fusion of the Hip: Through an anterior approach, the hip joint is disarticulated, and the remaining cartilage is removed from the head of the femur and the acetabulum. The head of the femur or remnants of the neck are then replaced, and a massive sinuous graft, 3 to 3½ inches (7.5 to 8.9 cm.) long and 1¼ inches (3.2 cm.) wide, consisting of both tables of the ilium, is removed from the crest. The graft is driven into a deep slot running through the ilium anteriorly, across the hip joint and through the head and neck into the shaft of the femur. Cancellous strips may be distributed about the denuded joint margin.

[**ED. NOTE:** Dislocation of the femoral head, in our opinion, is undesirable, because it destroys any reparative process that may have occurred.]

Femoroischial Fusion: In certain cases in which the head and neck of the femur have been totally destroyed and in which fibrosis has occurred in adduction and flexion, an oblique osteotomy is performed just above the level of the ischial tuberosity. The sharpened femoral stump is then implanted in the ischium. If the proximal fragment of the femur shows active tuberculous infection at the time of dissection, it may be removed. [**ED. NOTE:** This is an original procedure which should prove useful in the treatment of the advanced conditions for which it was designed.]

Anterior Decompression of the Spine: Most paraplegias associated with tuberculosis of the dorsal region of the spine are due to pressure of granulation tissue or of abscess pocket material extradurally, which is usually relieved as fusion occurs and disease activity subsides. Occasionally, however, such a paraplegia is due to fragmentation of a destroyed body caught between inclined surfaces of the vertebrae above and below and driven backward by the pressure of collapse to compress the spinal cord against the posterior arches. In these cases, the bony fragments, tuberculous granulation tissue and debris are removed by a costotransversectomy after fusion has become solid.

Fusion of the Knee: The method of Hibbs is used, in which the patella is mortised between the denuded ends of the femur and the tibia.

Fusion of the Ankle: A sliding graft from the tibia is moved downward and implanted into the astragalus after all cartilage has been removed from the ankle joint surfaces, including those of the malleoli. [**ED. NOTE:** This graft technic is not advisable for children in whom the lower epiphysial line of the tibia is still functioning.]

Fusion of the Shoulder: The cartilage is removed from the head of the humerus and the glenoid cavity through a saber cut incision just lateral to the tip of the acromial process. The under surface of the acromion is bared, and the humeral head is held in apposition to it by

two vitallium screws. Bone shavings are placed between the head and the glenoid cavity.

Resection of the Elbow Joint: This is preferred to arthrodesis because of the frequent complaint of the angulation of the upper extremity in cases in which fusion has been done. The joint of the elbow and its capsule and portions of bone about $\frac{3}{4}$ inch (1.9 cm.) each from the humerus and the forearm are resected through a posterior incision.

Fusion of the Wrist: Through a dorsal incision, curettage of the interarticular facets of the carpal bones and the radiocarpal joints is done as completely as possible. A massive sliding graft is then moved down from the radius and driven into the bases of the metacarpal bones, except the first. Slight dorsiflexing of the wrist holds the proximal end of the graft apposed to the radius. [ED. NOTE: This graft technic is not advisable for children in whom the lower epiphysial line of the radius is still open.]

Amputation: In the lower extremity the Grritti-Stokes amputation with its end-bearing stump is preferred. In the presence of massive tuberculous infections above the knee, midthigh amputations, even performed through purulent areas, have healed surprisingly well.

Amputation in the upper extremity is to be avoided if possible, because the crippling effect is so severe. Intractable pain due to contracting soft tissue, shutting off of the blood supply or complete destruction of a hand has occasionally justified routine amputations at various levels.

The importance of excision of the corresponding metacarpal bone when amputation of a finger is necessary is emphasized; this procedure leaves a better appearing and functioning hand.

Tuberculosis of the Hip.—Borellini⁸⁷ has observed 3 cases of tuberculosis of the hip which are of interest because of the unusual locations of the abscesses. In the first case, a girl of 12 had an abscess in the region between the iliac crest and the ribs; several fistulas developed here and in the vicinity of the sacroiliac joint. In another 12 year old girl an abscess and sinus appeared in the lumbosacral region and were traced to a tuberculous focus in the right hip. A boy 15 years of age presented a tuberculous sinus over the sacroiliac joint which was proved to have its origin in the ilium above the left hip.

Wassersug⁸⁸ reports 18 cases of tuberculous trochanteric disease, in 16 of which the diagnosis was confirmed. In 5 the trochanter alone was involved; in 2, only the bursas; in the others there was combined

87. Borellini, A.: Ossifluent Abscess: Unusual Evolution in Three Cases, Arch. di med. e chir. 9:65-76 (Feb.) 1940.

88. Wassersug, J. D.: Tuberculosis of Greater Trochanter and Trochanteric Bursae, J. Bone & Joint Surg. 22:1075-1079 (Oct.) 1940.

involvement. In 72 per cent there were other demonstrable tuberculous foci. There was a history of local trauma in many. Numerous operations were performed on 15 patients. Incision and drainage alone accomplished no permanent relief and were almost always followed by persistent sinuses. Radical excision or curettage was performed on 10 patients, and on their discharge from the hospital, six to ten months later, there were no draining sinuses or any disability from the lesion. The conclusion was that radical excision was the method of choice for treatment.

Tuberculosis of the Knee.—Haas⁸⁹ gives case reports of 12 children between the ages of $2\frac{3}{4}$ and $12\frac{1}{2}$ years who had fusion of the knee for tuberculosis. It usually required two operations to obtain solid fusion. The children were followed for an average of three and one half years, some of them for seven or eight years. In 8 there was no shortening; in the others there was only $\frac{1}{2}$ inch (1.27 cm.) or less of shortening.

Haas concludes that fusion of the knee can be performed in children as young as $2\frac{3}{4}$ years without any loss of growth.

Murray⁹⁰ made an investigation of 124 cases of tuberculosis of the knee joint picked at random from 2,922 cases of tuberculosis of joints. Biopsy was not done; the diagnosis was made solely on clinical and roentgen examination. All were followed for at least five years.

Thirty-three patients with synovial involvement only were treated conservatively with Thomas splints. Thirty per cent had a full range of motion at the time the study was made. Seventy with involvement of bone were treated first conservatively and then by excision. The operation resulted in ankylosis in only 45 per cent and had a mortality of 21 per cent.

The remaining patients apparently did not have tuberculosis of the knee joint at all but had "extra-articular involvement." [Ed. NOTE: Resection of the knee joint is liable to result in extreme shortening of the extremity in a child and, as shown in Murray's cases, is not at all certain to end in fusion. On the other hand, one of us (A. D. S.) has been successful, as was Haas, in obtaining arthrodesis in young children simply by removing the articular cartilage. In some of the cases, however, there was as much as 2 inches (5 cm.) shortening when growth was completed.]

Tuberculosis of the Ankle and Foot.—Mitchell⁹¹ studied the results of treatment of tuberculosis of the ankle and tarsus in 169 patients. The

89. Haas, S. L.: Growth Following Fusion for Tuberculosis of Knee in Children, *J. Bone & Joint Surg.* 22:1048-1053 (Oct.) 1940.

90. Murray, R. C.: Tuberculosis of Knee: Follow-Up Investigation of 124 Cases, *Brit. M. J.* 2:10-12 (July 6) 1940.

91. Mitchell, W. R.: End-Results and Treatment of Tuberculosis of Ankle and Tarsus, *Brit. J. Surg.* 28:71-81 (July) 1940.

outcome in those under 17 years of age was so different from that in the adults that the two groups were analyzed separately. He divided the 77 children into three groups. In the first two, those with extra-articular and those with synovial tuberculosis, none of whom was operated on, the results all were good. Sinuses developed in 77 per cent of the patients with intra-articular involvements. The treatment was by splints, and in only a few cases, in which operation was performed, was the diagnosis proved. Mitchell states that biopsy is not justified. Of the 45 adults only 12, or 27 per cent, were cured. The results were so bad that he concludes that for adults "conservative treatment should be tried only for a limited period, and if the response is not satisfactory, amputation should be performed without further delay." [ED. NOTE: The statistics of any series of cases in which the diagnosis has not been proved by pathologic examination are of little value, because of the large error which is inevitable. It is our opinion that biopsy in doubtful cases is essential. The results from arthrodesis both in children and in adults have been so satisfactory in the experience of one of us (A. D. S.) that amputation seems justifiable only in an occasional case of severe and advanced involvement.]

Tuberculosis of the Mandible.—Tuberculosis of the mandible is a rare disease. Meng⁹² reports 14 cases observed in seventeen and a half years at the Peiping Union Medical College Hospital, Peiping, China. Operative treatment consists of incision and drainage, sequestrectomy and partial ostectomy. There were tuberculous lesions in other bones in 43 per cent of the cases; and in 10 in which the chest was studied there was evidence of pulmonary or pleural tuberculosis. General antituberculous measures in the treatment are emphasized as well as local therapy to the mandibular lesion.

Tuberculosis of the Spine.—The question of spinal fusion as opposed to conservative treatment alone is discussed at length in articles read in a symposium at the meeting of the American Academy of Orthopaedic Surgeons in January 1940.

In speaking of the pathogenesis and medical treatment, Amberson⁹³ says that in the presence of vertebral tuberculosis a source in the chest should always be assumed and sought for, as well as hematogenous lesions in other systems, such as the serous membranes, the lymphatics and the genitourinary tract.

Treatment is aimed first at arresting hematogenous dissemination, diffusion of toxins from the vertebral lesions and the destructive pro-

92. Meng, C. M.: *Tuberculosis of Mandible*, J. Bone & Joint Surg. 22:17-27 (Jan.) 1940.

93. Amberson, J. B., Jr.: *Pathogenesis and Medical Treatment of Tuberculosis of Vertebrae*, J. Bone & Joint Surg. 22:807-814 (July) 1940.

esses of caseation and liquefaction. Later, adequate time should be allowed for complete healing, which may require several years. Healing cannot be accelerated materially except by rest treatment given according to its comprehensive meaning. For any form of tuberculosis surgical treatment usually is most effective ultimately, if it is postponed until the forces of resistance have become organized and the lesion has started to heal.

Mayer⁹⁴ gives his observations on 66 patients with tuberculosis of the spine who were treated over a period of fifteen years. All were children under 18 years of age. Thirty-seven were treated by spinal fusion and 29 without operation. Mayer states that there was little or no apparent difference in the end results in the two groups except that cure occurred 20 per cent later in those treated by operation. He states that if spinal fusion is done during the active stage of the disease it does not abbreviate the course but that if done during the reparative stage it has a beneficial effect. He believes that the general treatment of the systemic disease is more important than that of the local condition. [ED. NOTE: The conclusions from the study of this relatively small number of cases are contrary to those of the majority of surgeons. Except for 2 cases in which exploration revealed solid fusion, there is no critical study of the number of pseudoarthroses.]

Swett, Bennett and Street⁹⁵ give a report of a statistical study of 350 cases of tuberculosis of the spine from four different geographic areas. Patients of all age groups are included. Approximately half the group were treated conservatively. The length of follow-up study was from five to twenty-five years. The authors conclude that:

1. The present treatment of spinal tuberculosis is not satisfactory, because of the low percentage of cures, long duration of treatment and high mortality rate.

2. In general there is no advantage in operative as opposed to non-operative treatment.

3. The occurrence, behavior and disposal of the abscess are the dominant factors in the healing of Pott's disease. They found that the incidence of healing in all cases was 35 per cent, that in cases with persistent abscess it was 19 per cent and that in cases in which the abscess healed it was 59 per cent. They believe that further progress in the

94. Mayer, L.: Critical Study of Tuberculosis of Spine in Children. *J. Bone & Joint Surg.* **22**:875-877 (July) 1940.

95. Swett, P. P.; Bennett, G. E., and Street, D. M.: Pott's Disease—Incidence, Lesion, Relative Infrequency of Extension by Contiguity, Nature and Type of Healing, Role of Abscess, and Merits of Operative and Non-Operative Treatment. *J. Bone & Joint Surg.* **22**:878-894 (July) 1940.

successful treatment of the disease lies in the better understanding of this factor. [ED. NOTE: This report represents a careful study of a large number of cases. We believe that the value of the conclusions is lessened by the fact that no determination was made of the number of failures of fusion after operation. We are sure that this is necessarily high in any series and that unless these cases are detected and the defect repaired the results cannot be attributed to the method of treatment. Is not the failure of the abscess to disappear the result of the failure of the focus in the bone to heal, rather than the reverse?]

Cleveland⁹⁶ compares two groups of patients with tuberculosis of the spine, one treated at Sea View Hospital, a municipal institution on Staten Island, New York, where many patients with severe and advanced tuberculosis are seen, and the other treated at St. Luke's Hospital, New York. In all, there were 203 patients, admitted from 1924 to 1939. At Sea View Hospital the spine was affected in 52 per cent of 330 cases of tuberculous disease of the joints. Of the cases in which the spine was affected there was involvement of other joints in 15 per cent, and in these the results were the least favorable.

Cleveland emphasizes the importance of concomitant pulmonary and other tuberculous lesions in relation to the outcome by citing the mortality rates for various classes of patients as follows: (1) For those with no evidence of pulmonary tuberculosis, the mortality rate is 11.2 per cent; (2) for those with pulmonary tuberculosis but normal sputum and no spread to other organs, 7.2 per cent; (3) for those with pulmonary tuberculosis and evidence of tubercle bacilli in the sputum, 40 per cent; (4) for those with pulmonary tuberculosis and metastatic spread to other organs, 67.7 per cent.

There was the usual failure on the part of the physicians first examining these patients to recognize the disease early. Paraplegia occurred in 48 of 203 patients. Eleven were treated by laminectomy; 6 of these recovered their motor power. Of 31 having complete paraplegia, 42 per cent died.

Abscesses occurred in 68 per cent of 173 cases at Sea View Hospital and in only 23 per cent of 30 cases at St. Luke's Hospital. Roentgen evidence of abscess was present long before clinical signs in a high percentage of the cases. Sinuses were present in 22 per cent of the patients at Sea View Hospital, and 50 per cent of these patients died.

Spontaneous fusion occurred in 23 per cent of the cases at Sea View Hospital, and in this group the disease had been present for more than six years. In them the deformity usually was marked.

96. Cleveland, M.: Tuberculosis of Spine: Clinical Study of Two Hundred and Three Patients from Sea View and St. Luke's Hospital, *Am. Rev. Tuberc.* **41**:215-231 (Feb.) 1940; Treatment of Tuberculosis of Spine, *J. Bone & Joint Surg.* **22**:824-839 (July) 1940.

The spines of all the patients were fused by the Hibbs type of operation, and frequently reenforcement was provided with bone from the ilium or the tibia. Failure of fusion occurred in 15 of 203 cases, or 7.4 per cent. The importance of looking for this and repairing a defect when found is stressed. The necessity of doing fusion operations on infants and children is urged. Cleveland believes that his statistics prove this to be the treatment of choice for young patients. Fifty-five per cent of the 203 patients had excellent results; in 19 per cent the results were uncertain, and 25 per cent died. The per cent of recovery was higher and that of deaths lower in the patients at St. Luke's Hospital, probably owing to the fact that most of them were in the first two of the classes previously mentioned.

Cleveland points out that patients with active pulmonary disease may be treated by collapse therapy before fusion of the spine. He concludes that fusion of the spine hastens recovery and shortens the course of the disease.

Swift⁹⁷ presents a study of 584 patients with tuberculosis who had operations for spinal fusion at the New York Orthopaedic Dispensary and Hospital from 1911 to 1931 and who have been followed from five to twenty-four years or are known to have died. This number represents 71 per cent of the 817 patients with tuberculosis of the spine who were operated on in this period. For 61 per cent the length of follow-up was ten or more years.

Although in every case there are present a group of factors, such as the patient's power of resistance and the degree of virulence of the infecting organisms, that exert an influence on the course of the disease, there are certain demonstrable and expected benefits of a successful fusion. These are: (1) rest of the diseased area (the primary purpose and fundamental result of the fusion); (2) early subsidence of the activity of the lesion; (3) maintenance of the kyphos at a minimum of deformity; (4) growth of the vertebral bodies in the fused area in children to the extent potential in the growth factors which have survived the ravages of this disease; (5) possibility of the patient being ambulatory at an early date (87 per cent were up at the end of four months); (6) a permanent healthy roentgenographic appearance of the diseased vertebrae.

These effects are not observed in every patient. The two chief causes of an unsuccessful outcome are the inability of the patient's tissues to resist tuberculosis and the failure of the fusion to become solid or to

97. Swift, W. E.: End Results of Spine-Fusion Operation for Tuberculosis. *Spine, J. Bone & Joint Surg.* 22:815-823 (July) 1940.

cover a sufficient number of vertebrae. Pseudarthrosis occurred in 15 per cent of the cases.

Among the 584 patients there have been 168 known deaths (28 per cent). Fifty-three per cent were caused by some form of tuberculosis. This represents 88 persons and means that 15 per cent of the 584 died of tuberculosis. There were 7 operative deaths from shock, and 1 from shock and a streptococcic wound infection. Calculated on the basis of the 584 patients, the operative mortality was 1.4 per cent.

The patients with successful outcomes were divided into two groups: those who made an early recovery without complication and those who reached an excellent condition only after overcoming various complications, such as failure of the first operation to attain fusion. Of the children, 54 per cent had an early excellent result and 18 per cent, a delayed recovery. Of those over 11 years, 44 per cent had an early and 9 per cent a delayed good result.

The patients were also divided into children (1 to 10 years) and older patients (11 years or over). In both groups (the patients with uncomplicated and those with complicated recoveries) the results for children were better. The combined groups showed excellent results in 72 per cent of the children and in 53 per cent of the older patients.

In writing of the results of treatment of 39 children with tuberculosis of the spine at the Children's Memorial Hospital in Chicago, Chandler and Page⁹⁸ emphasized that the disease is a secondary pathologic lesion in a person with tuberculosis, and that healing is variable and dependent on the inherent immunity of the tissues, the reaction of the cellular elements adjacent to the lesion and the physicochemical processes involved in calcification. Recovery should not be referred to as healing, because the latter implies obliteration of the infecting organism. Collapse of the bodies facilitates healing, but an effort is made to keep the deformity at a minimum. Nutritional and hygienic measures are very important, and Chandler and Page wait for improvement in general before operating and stress the general after-care of the patient.

All patients came from unfavorable surroundings, and 36 per cent had a history of contact with a person with tuberculosis at home. Sixty-one per cent had a healed and 12 per cent an active pulmonary lesion. All of the patients were operated on by the Hibbs technic. Twenty-five patients, or 64 per cent, made a good recovery. In 3 the disease remained active. Paraplegia persisted in 1, and 6 died. The end result was unknown for 4.

98. Chandler, F. A., and Page, M. A.: Tuberculosis of Spine: End Result Series Studied at Children's Memorial Hospital, Chicago, *J. Bone & Joint Surg.* 22:851-859 (July) 1940.

The result of fusion of the spine in 396 cases of tuberculosis is given by Meyerding.⁹⁹ The patients were treated at the Mayo Clinic. The ages varied from 1 to 60, with the greatest number between 20 and 40. Four per cent were children. Three different types of spinal fusion were employed. All patients were followed for at least five years after operation. Good results were obtained in 63 per cent, all of whom were able to resume some form of occupation. Meyerding believes that spinal fusion combined with adequate conservative treatment is the treatment of choice but that this should not be done in an early stage of the disease, especially in children. He thinks that there is little choice in the methods of spinal fusion so far as the results go. The area fused must include all of the diseased vertebrae.

Harris and Coulthard¹⁰⁰ gave the results of the treatment of 80 patients with tuberculosis of the spine in a hospital for tuberculous patients in Toronto, Canada. Thirty patients were treated by rest alone because they were considered poor surgical risks. In them complications were common, and the mortality was high. The remaining 50 were treated by spinal fusion and rest. The operations were done from six months to three years after the rest treatment was started. Tibial grafts were fixed to the spinous processes by stainless steel wire. Rest in bed was continued for at least six months after operation. Bony ankylosis occurred in 66 per cent. Fracture of the graft occurred in 18 per cent. During the follow-up period, which was comparatively short, 12 per cent died. Ninety per cent of the patients had abscesses treated by repeated aspiration. Thirty per cent of the patients had active pulmonary tuberculosis.

Adams¹⁰¹ reviewed 63 cases of tuberculosis of the spine treated at the Lakeview State Sanatorium in Middleboro, Mass. All were followed for five years or more. The infections were of both the human and the bovine type, and a limited number of complications in the form of lesions in other organs were present. Debilitated patients were built up before operation. All the patients were operated on, some by the Hibbs technic but the majority by the Albee bone graft. Thirty-eight patients recovered, and twenty-five died. Adams states that for those who did recover the period of healing was long.

99. Meyerding, H. W.: Tuberculosis of Spine: Treatment and Results. *J. Bone & Joint Surg.* 22:840-850 (July) 1940.

100. Harris, R. I., and Coulthard, H. S.: End-Results of Treatment of Pott's Disease. *J. Bone & Joint Surg.* 22:862-874 (July) 1940.

101. Adams, Z. B.: Tuberculosis of Spine in Children: Review of Sixty-Two Cases from Lakeville State Sanatorium. *J. Bone & Joint Surg.* 22:880-891 (July) 1940.

Rosenbaum¹⁰² gives the result of spinal fusion in 100 cases of tuberculosis in children. He does not state the length of time that the patients were followed after operation. Various operative technics were used. His plan was to give general supportive treatment for a minimum of two years and to perform the operation only after the patient had reached the quiescent or recuperative stage. His results were extraordinarily good, including decrease or arrest of deformity in 94 per cent of the cases, improvement of paraplegia in 76 per cent and healing in 89 per cent.

[ED. NOTE: The number or fate of those patients whose condition did not become quiescent and who therefore were not subjected to operation is not given. We believe that operation should be postponed until the patient's general condition is reasonably good but that to wait until the disease is quiescent is a mistake, because in some cases it never reaches this stage.]

V. INFECTIONS OF BONES AND JOINTS, EXCLUSIVE OF TUBERCULOSIS

General Considerations.—While nontuberculous infections of bones and joints are caused in the main by the staphylococcus and the streptococcus, Valentini¹⁰³ points out that there is a variety of less frequently encountered organisms which also may be causes. In the early stages of diseases of bones and joints the clinical features may have certain differences depending on the organism present, but as a general rule roentgenograms will show primarily bone destruction in the tuberculous infection and both bone production and bone destruction in the non-tuberculous.

Hanke¹⁰⁴ states that there are two routes of infection, the hematogenous and the exogenous; the former is the more common in peace times. He feels it is important to determine which organism is responsible and points out that in most cases the streptococcus does not produce necrosis, whereas the staphylococcus nearly always produces both necrosis and sequestration.

Toye¹⁰⁵ emphasizes that orthopedic surgeons must become "osteomyelitis conscious." In this way diagnosis can be made earlier and treatment begun before much local bone damage can occur.

102. Rosenbaum, M. G.: Tuberculosis of Spine, *Southwestern Med.* **24**:123-125 (April) 1940.

103. Valentini, F. B.: Therapy of Articular Suppurations with Special Reference to Early Form, *Policlinico (sez. chir.)* **47**:41 (March) 1940.

104. Hanke, H.: Acute Osteomyelitis, *Med. Klin.* **36**:80-82 (Jan. 19) 1940.

105. Toye, J. E.: Acute Hematogenous Osteomyelitis: Diagnosis and Treatment, *J. M. Soc. New Jersey* **37**:51-53 (Feb.) 1940.

Le Cocq¹⁰⁰ emphasizes the tendency of the bacteria to lodge in the deeper channels next to the epiphysial line, where phagocytosis is least active.

Rantz¹⁰⁷ reports a case of suppurative arthritis of the knee and the hip due to streptococci of the Lancefield group B, which have rarely been found infecting human beings. He states that the disease usually starts in the metaphysis or cancellous end of the diaphysis, where the circulation is relatively sluggish, and spreads locally to involve the adjacent shaft by stripping the periosteum or, if the epiphysis is intra-articular, perhaps spreads into the adjacent joint.

Martin and Picquart¹⁰⁸ point out that children up to the age of 3 years are particularly susceptible and that the disease in this age group is clinically different from osteomyelitis in adults. They say that epiphysitis is the most characteristic lesion in infancy. The first stage consists of vascular injection of varying duration; suppuration occurs during the second stage with the clinical features of high fever, pain and swelling at or near the joint and evidences of general constitutional toxicity. The disease then erodes into the joint, resulting in deformity and a tendency to pathologic subluxation or dislocation.

Valentini¹⁰⁹ reports 5 cases of acute suppuration of the synovial membrane and states that the joints were involved in the following order: knee, ankle, hip and shoulder. The mortality rate was highest in the cases in which the shoulder was affected.

From a review of the literature Lauber¹⁰⁹ also finds the knee is the most frequently involved. He cites Wiesmann,^{109a} who observed that in 52 per cent of his cases the portal of entry was the skin, and in 15 per cent, the tonsils. While various types of organisms may be found as the infecting agent, Hanke¹⁰⁴ feels that other factors play a definite part and that the body's resistance to the disease may be dependent on whether or not there is a deficiency of vitamin C. In addition, there is a physical incidence as well as a geographic distribution, and he treats of the relation of previous trauma to the development of osteomyelitis. He states that trauma can be admitted as a common causative factor only if it is of sufficient severity to produce a manifest injury to the affected bone, and then only if the osteomyelitis develops within twenty-four to seventy-two

106. Le Cocq, J. F.: *Diagnosis and Treatment of Acute Osteomyelitis*, *New York West Med.* **39**:171-172 (May) 1940.

107. Rantz, L. A.: *Suppurative Arthritis Due to Hemolytic Streptococci of Lancefield Group B: Case Report*, *Ann. Int. Med.* **13**:1744-1747 (March) 1940.

108. Martin, A., and Picquart, A.: *Osteomyelitis in Children*, *Semaine de Med. de Paris* **16**:58-64 (March) 1940.

109. Lauber, H. J.: *Therapy of Empyema of Knee with Review of Literature*, *Med. Klin.* **36**:360-361 (March 29) 1940.

109a. Wiesmann, E.: *Problem of Pyemic Metastases into Joints*, *Dtsch. Ztschr. f. Chir.* **249**:224-255. 1937.

hours after the trauma. Colonna¹¹⁰ feels that in acute hematogenous osteomyelitis the disease in the bone is always secondary to an infection elsewhere in the body.

Bordasch¹¹¹ has studied the bactericidal power of bone marrow under the influence of external agents in his experiments on rabbits, and he concludes that a blunt injury of the shaft of a long bone produces a marked and prolonged increase in the bactericidal power of the bone marrow at this site. He states that the bactericidal power of the bone marrow in any part of the body is considerably greater after hemorrhage than after trauma to a bone and about twenty times greater after hemorrhage than when the marrow is normal. These interesting experiments led him to conclude that in cases of extreme malnutrition and starvation the bactericidal power of the bone marrow is increased even more than after hemorrhage and is about thirty times more than that of normal bone marrow.

Rosenbach¹¹² has found that trauma is an infrequent cause of osteomyelitis; although clinical observations may disclose injury as a frequent precursor, an actual source of infection, such as an open fracture, a furuncle or an infected wound, must be demonstrated. However, he reports 2 cases in which trauma alone seemed to be the initiating factor. One patient was a boy who injured both knees while exercising; osteomyelitis developed in both tibias a few days later. In the second case there was an injury to the ankle, and fourteen days later osteomyelitis developed in the lower end of the tibia. The criteria of traumatic osteomyelitis, he states, have been laid down by Liniger and are as follows: (1) The accident must be demonstrated; (2) there must have been considerable action on the subsequently diseased bone; (3) the disease must have originated in immediate association with the injury. Therefore, it is obvious that the relation of trauma to osteomyelitis can seldom be clearly demonstrated.

Beckman and Sullivan¹¹³ feel that every attempt should be made to recognize the type of organism causing the infection before treatment is begun, as streptococcic septicemia behaves differently from staphylococcic in both its general and its local reactions. Because one is dealing with a bacteremia in these cases, the best results are obtained when the lesions of bones and joints are treated by conservative surgical measures

110. Colonna, P. C.: Acute Hematogenous Osteomyelitis, *J. Kansas M. Soc.* **40**:493-498 (Dec.) 1939.

111. Bordasch, F.: Experimental Study of the Bactericidal Effect of Bone Marrow, *Deutsche Ztschr. f. Chir.* **253**:237-262, 1940.

112. Rosenbach: Osteomyelitis and Trauma, *Monatschr. f. Unfallh.* **46**:597-605 (Dec.) 1939; abstracted in Painter, C. F.: Year Book of Industrial and Orthopedic Surgery, Chicago, The Year Book Publishers, Inc., 1940, p. 38.

113. Beckman, F., and Sullivan, J. E.: Blood-Borne Pyogenic Infections of Bones and Joints, *Ann. Surg.* **111**:292-314 (Feb.) 1940.

alone and more attention is paid to the general condition of the patient and supportive measures employed. [Ed. NOTE: We are in complete agreement.] In their 21 cases of pyarthrosis in acute osteomyelitis, aspiration of the joint one or more times or incision to relieve tension, immobilization of the extremity and infrequent dressings proved to be of decided benefit.

McCoy and Ross¹¹⁴ feel that in cases of acute hematogenous osteomyelitis the prognosis can be based on the presence or absence of a positive blood culture, on the type of organism found and on the number of colonies found if the blood culture is positive. In addition to surgical drainage and immobilization, the administration of staphylococcic anti-toxin is recommended by these authors. While in the average case osteomyelitis develops in the metaphysial region of the bone, Paltrinieri¹¹⁵ describes cases of chronic diaphysial osteitis of the bone and states that this condition may begin in childhood or adolescence with a deep severe pain, usually in one of the long bones and associated with more or less circumscribed tumefaction. In diaphysial involvement, the organism is usually the staphylococcus and the typical lesion is a small excavation of the cortex, which is filled with pus and sometimes contains a small sequestrum. This condition must be differentiated from tuberculosis, typhoid or Ewing's bone tumor.

Brodie's Abscess.—Cousineau¹¹⁶ reviews in detail the condition first described by Brodie and since known as Brodie's abscess. Cousineau states that in 1765 Davis described what was probably the same condition. Brodie's abscess is a local chronic bone abscess. It occurs mostly in persons under 15 years of age during the period of active growth. Boys are more frequently affected than girls; in order of frequency the bones affected are the lower end of the femur, the humerus and the radius. Trauma must be a very real factor in the production of the abscess. The cavity has usually been found to contain staphylococci, but typhoid and colon bacilli have been isolated. Cousineau points out that many times the contents are sterile. The treatment recommended is opening the wound and cleaning it out thoroughly; then it is tightly closed.

Sclerosing Osteitis of Garré.—Another form of infection of bone is the chronic, diffuse sclerosing osteitis of Garré, which is described by Toumey.¹¹⁷ This condition manifests itself by a dull ache in the region

114. McCoy, R. H., and Ross, D. E.: Acute Hematogenous Osteomyelitis. *Canad. M. A. J.* **42**:162-168 (Feb.) 1940.

115. Paltrinieri, M.: Circumscribed Cortical Osteitis. *Chir. d. org. d. inf.* **25**:407-416 (April) 1940.

116. Cousineau, P.: Brodie's Abscess. *Ann. méd.-chir. de l'Hôp. Sainte-J.* **3**:145-154 (May) 1940.

117. Toumey, J. W.: Sclerosing Osteitis of Garré. *S. Clin. North Am.* **20**:857-861 (June) 1940.

involved, usually worse at night. It should be differentiated from syphilitic periostitis, osteogenic sarcoma, Ewing's sarcoma and hyperparathyroidism. Dusting sulfanilamide powder into the saucerized wound followed by complete closure is recommended.

Syphilis.—Evans ¹¹⁹ discusses syphilis of bones and joints in infants. He feels that the diagnosis of congenital syphilis may be difficult to make and that in most cases it is either finally confirmed or excluded by serologic studies or by roentgen examination of the long bones. A positive reaction, he states, is of doubtful validity, as it is known that the property of producing a positive reaction may be transferred from the maternal blood to the fetal blood without the fetus being syphilitic. On the other hand, the negative serologic reaction of a newborn child is also inconclusive, for many children who eventually show evidence of syphilis have negative serologic reactions at birth.

Evans also points out that bands of rarefaction or condensation in the diaphysis are frequently seen in roentgenograms, especially in those of premature infants and ones with nutritional disturbances. These cannot, however, be regarded as specific for syphilis. The periosteal shadows, varying from a fine white line parallel to the long bones and most commonly observed in the femur to heavy onion-like cloaking of the bone, have been considered in the past as pathognomonic of syphilis, but Evans feels that they are not, as these appearances may be found in subperiosteal fractures occurring at delivery. Rickets, tuberculosis and other forms of osteomyelitis make the diagnosis of congenital syphilis difficult.

McDonald and Sellers ¹²⁰ feel that roentgenograms will detect syphilis of the bone in most cases by the time the infant has reached the age of 6 weeks. Hill in discussing this paper says that the roentgenographic characteristics of congenital syphilis, namely, periostitis and destruction in the ends of bones along with smooth, condensed and irregular epiphysial lines, should not be confused with the signs of either scurvy or rickets. Scurvy will not show changes in the bones before the fifth month and therefore need not be considered at all during the first two months. Brown in this same discussion says that, while there is always multiple osseous involvement, not all the bones are affected. Therefore, he advises a study of the whole bony system in every case; this in his opinion would permit congenital syphilis to be discovered within the first two or three months of life.

118. Footnote deleted by author.

119. Evans, W. A., Jr.: *Syphilis of Bones in Infancy: Some Possible Errors in Roentgen Diagnosis*, J. A. M. A. **115**:197-200 (July 20) 1940.

120. McDonald, D. H., and Sellers, E. D.: *Pulmonary and Bony Changes in Congenital Syphilis*, Texas State J. Med. **35**:838-840 (April) 1940.

Thomason and Mayoral¹²¹ state that syphilitic periostitis is usually a secondary or tertiary phenomenon and seldom occurs before two years after the initial infection. However, some authors have described it as occurring at the same time or from two to fifteen weeks after the infection. Syphilitic periostitis according to Thomason and Mayoral affects primarily adults between the ages of 20 and 40; the shafts of the long bones and the outer table of the skull are most frequently involved. The disease may be congenital, but this is not the usual form. In patients with osseous lesions injection of arsphenamine is followed by intense pain for twelve to twenty-four hours and then prompt relief, perhaps the first in months. If, however, the whole bony structure is involved rather than the periosteum only, the disappearance of the signs and symptoms may be much more gradual and require days or weeks, during which there will be little if any objective change in the osseous lesions. The patient with syphilitic infection of bones should be kept under observation indefinitely, and special emphasis must be placed on periodic examinations of the heart and aorta as long as the patient lives.

In discussing syphilis of the joints, Freund¹²² stresses the intra-articular hemorrhage and effusion that may be produced in the joint, stating that the normal joint pressure is negative but that under certain conditions it may increase to a positive value of 70 mm. of water. This, he says, will cause injury to the underlying bone, particularly hemophilic arthritis, in which there may be destruction of the whole epiphysis.

Gandola¹²³ reports syphilitic tenovaginitis in a man of 30 with a noncontributory family history who had suffered for one month from a lesion of the prepuce and during the second stage from a swelling of the right hand and forearm. After treatment for a few days with an insoluble bismuth preparation the patient improved and after the second injection became well. The symptoms subsided in less than one month.

Fungous Infections.—Krumdieck and Stevenson¹²⁴ report 1 case of actinomycosis characterized by spinal epidural abscess. Postmortem examination revealed the abscess involving the right side in the thorax, the chest, the vertebrae and the liver. Hurst¹²⁵ reports a case of actinomycosis involving the retina, the lungs and the vertebrae. The diagnosis in this case was not made until autopsy, although the sulfur granules

121. Thomason, H. A., and Mayoral, A.: Syphilitic Osteomyelitis, *J. Bone & Joint Surg.* **22**:203-206 (Jan.) 1940.

122. Freund, E.: Pathologic Significance of Intra-Articular Pressure, *Edinburgh M. J.* **47**:192-203 (March) 1940.

123. Gandola, M.: Tendovaginitis in Secondary Period, *Gazz. d. osp.* **61**:241-245 (March) 1940.

124. Krumdieck, N., and Stevenson, L. D.: Spinal Epidural Abscess Associated with Actinomycosis, *Arch. Path.* **30**:1223-1226 (Dec.) 1940.

125. Hurst, J. H.: Actinomycosis Progressively Involving Retina, Lungs and Vertebrae, *M. Bull. Vet. Admin.* **17**:90-92 (July) 1940.

were found in the pus discharged from the sinus. He feels there is little evidence that actinomycosis is contagious and believes the infection takes place by implantation of the parasite in the tissues by a foreign body, it being widespread among cattle and pigs. He says statistics indicate that the disease is prevalent in the upper part of the Mississippi Valley and the northwest section of the United States. Craig, Dockerty and Harrington¹²⁶ discuss a case of intravertebral and intrathoracic blastomycosis.

Undulant Fever.—Steindler¹²⁷ in discussing the orthopedic complications of undulant fever states that one may divide the metastatic lesions of the locomotor system into three groups: those of pyogenic character involving a single joint, those of the serous type with polyarthritic dissemination and those with osteomyelitis. All brucellar lesions are late sequelae of the infection, occurring eight to twelve weeks after the acute onset and having a definite tendency to self limitation. Osteomyelitis of the vertebra is by far the most frequent complication, usually involving the lumbar portion of the spine. Steindler states that up to 1939, 57 cases were reported in the literature, and he adds 4 more. The characteristic features of the skeletal involvement in brucellosis are: preference for the lumbar region of the spine with narrowing of the joint spaces and some reactive bone production; rarity of formation of abscesses; a rather benign course, and response to conservative treatment by rest and immobilization. An enlarged spleen, a low white blood cell count, negative tuberculin and Wassermann reactions and a history of remittent fever, chills and sweating are of importance in the differential diagnosis. A positive agglutination for *Brucella* in the higher dilutions will usually be observed.

Echinococcic Cyst.—Among the rare nontuberculous infections involving the joints and soft tissues is that caused by *Echinococcus granulosus*. Mason¹²⁸ reports a case of recurring echinococcic cyst of the thigh and states that one of the sources of this infestation is the hands. These are soiled in petting an infected dog that has become contaminated by eating the viscera of a sheep, an ox or a pig. In this way the covered eggs are swallowed. After these eggs bore through the intestinal wall, they get into the portal circulation and finally reach the pulmonary circulation. He believes that infestation occurs in childhood in a great majority of cases and that the cyst may thus be nearly

126. Craig, W. M.; Dockerty, M. B., and Harrington, S. W.: Intravertebral and Intrathoracic Blastomycoma Simulating Dumb-Bell Tumor, *South. Surgeon* 9:759-766 (Oct.) 1940.

127. Steindler, A.: Orthopedic Complications of Brucellosis, *J. Iowa M. Soc.* 30:256-257 (June) 1940.

128. Mason, J. B.: Recurrent *Echinococcus* Cyst of Thigh, *Surgery* 7:407-409 (March) 1940.

as old as the patient. Diagnosis is easy when an echinococcic epidemic occurs. Mason feels that roentgenograms combined with the complement fixation test of Fairley are useful in the diagnosis. Treatment is unsatisfactory, although complete removal of the cyst is the method of choice.

Lesions of the Vertebra.—In the discussion of osteomyelitis involving the vertebrae, Alexander¹²⁹ reports cases in which it occurred in the cervical region and maintains that it is more common than ordinarily supposed. He feels that men have osteomyelitis in the cervical vertebrae twice as frequently as women and that it is found in the second and third decades especially. The causative organisms are chiefly *Staphylococcus aureus*, *Staphylococcus albus* and *Streptococcus pyogenes*. Schein¹³⁰ describes a case in which *Bacillus pyocyaneus* was the positive organism. The infection occurred after a cystoscopic examination. Schein feels that while this organism is generally only mildly pathogenic it may become a dangerous invader after instrumentation of the genitourinary tract. Immobilization by a plaster jacket and chemotherapy were used in the treatment, and apparently the condition was cured. Sacrococcygeal osteomyelitis is described by Bacon and Taylor,¹³¹ who report 2 cases in which the condition simulated anorectal fistula. The best treatment, according to them, consists of removal of the involved bones with wide exposure, the large wound being allowed to granulate slowly. Mathe¹³² discusses osteomyelitis of the pelvic girdle. In the case he reports there was an associated vesical fistula. He considers the genitourinary problem involved in the management of such a case greatly complicated whenever intractable cystitis is present.

Syphilitic lesions of the spine are rare and may be mistaken for Pott's disease. Weber and Carrión¹³³ report a case of syphilitic spondylitis. The patient was a man of 30 with a paravertebral abscess and with roentgenographic evidence of destruction of bone. Two years later a draining sinus developed in the neck, and roentgen examination showed destructive osteitis of the body of the atlas. Weber and Carrión point

129. Alexander, R. J.: Chronic Osteomyelitis of Cervical Vertebrae. *Rock. Mountain M. J.* **37**:753-757 (Oct.) 1940.

130. Schein, A. J.: *Bacillus Pyocyaneus* Osteomyelitis of Spine: Report of Case of Successful Treatment with Sulfanilamide, *Arch. Surg.* **41**:740-746 (Sept.) 1940.

131. Bacon, H. E., and Taylor, A.: Osteomyelitis of Coccyx and Sacrum with Sinus Formation Simulating Ano-Rectal Fistula: Report of Two Cases. *England J. Med.* **223**:668-671 (Oct. 24) 1940.

132. Mathe, C. P.: Management of Intractable Cystitis Associated with Vesical Fistula and Osteomyelitis of Pelvic Girdle: Report of Three Cases. *Am. J. Urol.* **43**:547-554 (Oct.) 1940.

133. Weber, L. A., and Carrión, C. J.: Case of Syphilitic Spondylitis of Cervical Spine, *Semana méd.* **1**:94-97 (Jan. 11) 1940.

out that Wassermann and Kahn tests should always be done in any case in which there is a destructive spinal lesion, and in their case a Calot jacket and specific treatment sufficed to cure the patient after two years.

Lesions of Femur.—Moss¹³⁴ discusses osteomyelitis of the femur and reports 11 cases of acute osteomyelitis of the femoral neck, in 7 of which there were the clinical signs of pain on pressure just below the midline of Poupert's ligament and associated with a flexion of the right thigh on the abdomen with a limited range of pain-free motion in the hip joint proper.

Cysts may develop in the popliteal space owing to chronic osteomyelitis of the femur. Borellini¹³⁵ reports such an occurrence in a woman aged 30. The disease manifested itself at the age of 6. At this time the knee became swollen without apparent cause, and there was severe and continuous pain. After about a month the patient became symptom free. Many years later the pain reappeared, and a tumor, which was the size of an orange and red and painful to touch, formed on the internal surface of the right knee. Aspiration revealed a yellowish fluid; bacteriologic tests were negative, and roentgenograms revealed chronic osteomyelitis of the right femur. After incision and drainage with curettage of the bone, primary healing occurred.

Mazzini and Carman¹³⁶ report a case of brucellosis and state that involvement of joints is far more common than osteomyelitis. They believe this is the first reported case from Argentina. Their patient had worked a number of years in the meat-packing industry. After a cut on his finger, a local infection developed, from which he completely recovered, although he was proved to have undulant fever. Three months later osteomyelitis of the femur developed; culture yielded *Brucella suis*. This case is of further interest because under the workmen's compensation law of Argentina brucellosis is considered an occupational disease and therefore the patient is entitled to compensation.

Lesions of the Knee.—Lauber¹⁰⁹ discusses suppurative arthritis of the knee joint. He feels that while the staphylococcus is the most frequent offender the streptococcus or practically any of the other organisms may occasionally be the cause. While he reviews the different types of treatment, he advocates conservative expectant treatment; however, all periarticular abscesses should be incised. If arthrotomy becomes necessary the author holds that drainage should be extra-articular and that

134. Moss, W.: Osteomyelitis of Upper End of Femur: Description of Diagnostic Sign, New Orleans M. & S. J. 92:569-572 (April) 1940.

135. Borellini, A.: Cysts of Popliteal Space Due to Chronic Osteomyelitis, Arch. di med. e chir. 9:289-296 (June) 1940.

136. Mazzini, O. F., and Carman, D. R.: *Brucella Osteomyelitis of Femur*, Prensa méd. argent. 27:517-520 (March 6) 1940.

the use of an iodoform gauze pack or any foreign body in the joint should be strongly discouraged.

Kendrick¹³⁷ reports favorable treatment of a patient with septic arthritis of the knee joint by the oral administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine) combined with multiple aspirations of the joint. The patient was a boy of 14 years of age. The blood and synovia were positive for Staph. aureus, and sulfapyridine was found to be much more effective than sulfanilamide in fighting the infection. This patient left the hospital on the twenty-eighth day with a full range of motion and no tenderness.

Henson¹³⁸ recommends the use of oxygen in preventing adhesions in acute infections of joints. He advises withdrawing as much fluid as possible and allowing the oxygen to flow into the joint to the point tolerated by the patient. Compression is maintained several minutes at the point where the needle is removed to prevent the escape of oxygen. He reports that no accident of any kind occurred in his series of 150 cases.

Beutel¹³⁹ describes a case of gumma of the patella in a woman of 48 who had injured her knee five years before. She had a strongly positive Wassermann reaction. A shallow impression with a light area of sclerosis and annular hyperostosis were noted in the patella.

Lesions of the Leg.—In a discussion of osteomyelitis of the tibia it should be mentioned that Weaver and Francisco¹⁴⁰ point out that in their opinion the pseudofracture of the tibia, described in 1939 by Roberts and Vogt,¹⁴¹ should not be called a fracture. They report 3 of their own cases and feel that from the history, physical findings, roentgen and pathologic reports their cases are consistent with a type of nonsuppurative osteomyelitis. Nédelec¹⁴² reports a case in which there was subperiosteal resection of the entire tibial diaphysis for osteomyelitis. The patient was a child of 10 who showed no signs of bone regeneration.

137. Kendrick, J. I.: Staphylococcus Septicemia with Septic Arthritis of Knee Treated with Sulfapyridine: Report of Case, *Cleveland Clin. Quart.* 7:35-36 (Jan.) 1940.

138. Henson, J. B.: Use of Oxygen in Preventing Adhesions from Trauma and Infection, *South. M. J.* 33:776-778 (July) 1940.

139. Beutel, A.: Gumma of Patella, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 11: 591-592 (Oct.) 1939; abstracted in Painter, C. F.: *Year Book of Industrial and Orthopedic Surgery*, Chicago, The Year Book Publishers, Inc., 1940, p. 43.

140. Weaver, J. B., and Francisco, C. B.: Pseudofractures: Manifestations of Non-Suppurative Osteomyelitis, *J. Bone & Joint Surg.* 22:610-615 (July) 1940.

141. Roberts, S. M., and Vogt, E. C.: Pseudofracture of Tibia, *J. Bone & Joint Surg.* 21:891-901 (Oct.) 1939.

142. Nédelec: Diaphysial Resection in Osteomyelitis: Pseudoarthrosis Treated by Hahn-Hutington Operation, *Mém. Acad. de chir.* 66:316-320 (Mém. 1940, April 3) 1940.

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alcohol, and after the wound is dry, a bismuth-iodoform paste is applied to all bone and muscle tissue. The paste is then covered with a transplant of fat, so the wound is closed without tension. The formula he recommends for the paste is 1 part bismuth subnitrate and 2 parts iodoform with sufficient liquid petrolatum to make a thick paste.

Of the complications to be watched for in osteomyelitis of the bones and joints are pathologic fractures with subsequent dislocation of the involved joint; for this reason Nicholson¹⁶¹ stresses the importance of immobilization of the joint early in the disease to lessen the opportunity for dislocations. General toxemia must be combated and adequate drainage obtained. He feels that sulfanilamide and sulfapyridine have proved of great value. He cautions against early weight bearing and stresses the value of careful follow-up in cases of septic arthritis.

Valentine and Butler¹⁶² have investigated the degree of immunity in patients with recurrence of infection after war wound osteomyelitis and recommend the use of toxoid. The dosage is gradually built up in weekly injections until the patient can take a maintenance dose of 0.3 cc. of undiluted toxoid intramuscularly in the deltoid muscle. However, they say there has not been time to evaluate this treatment with reference to preventing further recurrence.

In the preliminary report, Marcus and Groh¹⁶³ recommend the use of roentgen therapy in the treatment of acute osteomyelitis of the fingers and toes. They report 10 cases of infection and osteomyelitis of the phalanges. They believe the response to roentgen treatment is prompt, and early treatment will often prevent complicated osteomyelitis.

VI. CHRONIC ARTHRITIS

Gold Salts.—Numerous preparations of gold salts for the treatment of chronic arthritis have been receiving much critical appraisal from investigators and members of clinic staffs in many lands.¹⁶⁴ The purpose

161. Nicholson, J. T.: Septic Arthritis of Hip: Treatment by Immobilization, *Pennsylvania M. J.* 43:950-955 (April) 1940.

162. Valentine, F. C. O., and Butler, E. C. B.: Toxoid Treatment of Recurrent Infection After Staphylococcal Osteomyelitis, *Lancet* 1:914-917 (May 18) 1940.

163. Marcus, A., and Groh, J. A.: X-Ray in Treatment of Acute Osteomyelitis of Fingers: Preliminary Report, *Indust. Med.* 9:551-554 (Nov.) 1940.

164. (a) Osgood, R. B.: Medical and Social Approaches to the Problem of Chronic Rheumatism, *Am. J. M. Sc.* 200:429-445 (Oct.) 1940. (b) Ruiz Moreno, A.: Chrysotherapy of Rheumatoid Arthritis: Indications and Technic, *Arch. urug. de med.* 16:301-312 (April) 1940. (c) Mester, A.: Chrysotherapy of Chronic Polyarthritis, *Rev. argent. de reumatol.* 4:290-293 (Jan.) 1940. (d) Hoegh-Guldberg, O.: Sodium Gold Thiosulfate in Chronic Polyarthritis in Rural Practice, *Ugesk. f. læger* 102:500-505 (May 16) 1940. (e) Raymundo, B. A.: Gold Salts in Arthritis, *An. Inst. modelo de clín. méd.* 19:140-163, 1939.

has been either to find a nontoxic salt¹⁶⁵ or to protect the patient from the dangerous toxic effects of the gold. Liver extract, vitamin C¹⁶⁶ and variation of the amount of the doses of gold salts have been tried. Ellmann, Lawrence and Thorold¹⁶⁷ report their observations of 90 patients divided into experimental and control groups. Their results show that large doses of gold salts lead to inactive phases of the disease. In 47 per cent of those receiving large doses and 27 per cent of those receiving small doses the disease became inactive. Sixty-six per cent of those receiving large doses and 59 per cent of those receiving small doses showed reduced swelling about the infected joint. However, although according to most authors gold preparations make rheumatoid arthritis inactive in a large percentage of the cases, they are dangerous drugs because they seriously damage the kidneys, the intestines, and the skin and have caused deaths. Some physicians have felt it necessary to safeguard themselves by requiring patients to sign their release from all responsibility for the possible complications.¹⁶⁸

Gold is excreted slowly and may not have left the body even six months after its administration has been discontinued. Its use should be stopped when the sedimentation rate is below 12 mm.¹⁶⁷ [ED. NOTE: Carefully controlled experiments are being carried out in many clinics to find if possible the correct way to use gold salts.]

Sulfur Treatment.—This form of treatment has lost favor during the last year. Freyberg, Block and Fromer,¹⁶⁹ Abrams and Bauer¹⁷⁰ and Cawadias¹⁷¹ have found no sulfur deficiency and see no need for its use. Freyberg has even suggested that the treatment might be harmful.¹⁶⁹

165. (a) Sabin, A. B., and Warren, J.: Therapeutic Effectiveness of Practically Non-Toxic New Compound (Calcium Aurothiomalate) in Experimental, Proliferative, Chronic Arthritis of Mice, *Science* **92**:535-536 (Dec. 6) 1940. (b) Driscoll, R. E., and Markson, D. E.: One Hundred Cases of Arthritis Treated with Comparatively Non-Toxic Gold Compound, Illinois M. J. **78**:503-504 (Dec.) 1940. (c) Hansen, A. C.: Treatment of Atrophic Arthritis, Wisconsin M. J. **39**:106-108 (Feb.) 1940. (d) Hoegh-Guldberg.^{164d}

166. Secher, K.: Vitamins as Supplement to Sanocupin in Arthritis, *Lancet* **1**:735-736 (April 20) 1940; Sanocupin and Vitamin C in Therapy of Arthritis and Tuberculosis, *Nord. med. (Hospitalstid.)* **6**:821-832 (April 27) 1940.

167. Ellmann, P.; Lawrence, O. S., and Thorold, G. P.: Gold Therapy in Rheumatoid Arthritis, *Brit. M. J.* **2**:314-316 (Sept. 7) 1940.

168. Comroe, B. I.: Arthritis and Allied Conditions, Philadelphia, Lea & Febiger, 1940.

169. Freyberg, R. H.; Block, W. D., and Fromer, M. F.: Study of Sulfur Metabolism and Effect of Sulfur Administration in Chronic Arthritis, *J. Clin. Investigation* **19**:423-435 (March) 1940.

170. Abrams, N. R., and Bauer, W.: Treatment of Rheumatoid Arthritis with Sulfur: Critical Evaluation, *New England J. Med.* **222**:541-546 (March 28) 1940.

171. Cawadias, A. P.: Sulphur Treatment in Endocrine Metabolic Arthritides, *Brit. J. Rheumat.* **2**:125-129 (Jan.) 1940.

Wheeldon,¹⁷² however, still finds sulfur as used in his clinic of real value.

Sulfanilamide Treatment.—Sulfanilamide appears to be effective only in gonorrheal arthritis; it does not help in other types.¹⁷³

Treatment with Vitamins.—There is increasing proof of general vitamin deficiency in chronic rheumatoid arthritis. Hall, Bayles and Soutter¹⁷⁴ have seen no improvement after eight months of use of vitamin A. The requirements of patients with rheumatoid arthritis were found to be four to ten times the normal amount in the diet. Opinions vary as to the use of vitamin D. Muether^{175a} considers it dangerous. Snyder and Squires¹⁷⁶ believe it beneficial when given in large doses. The vitamin B complex and vitamin C have been found useful.¹⁷⁵ Jacques¹⁷⁷ feels that vitamin C has no effect on rheumatoid arthritis.

Röntgen Treatment.—This form of treatment has for many years been successfully used by Kahlmeter, of Stockholm, who claims excellent results.¹⁷⁸ His work has stimulated its use in this country. In spite of many studies no one yet knows to just what the beneficial effects are due. Smyth, Freyberg and Peck¹⁷⁹ treated 100 patients. The majority of these had characteristic rheumatoid arthritis; others had rhizomelic spondylitis, degenerative disease of joints or so-called fibrositis. They were given roentgen therapy to some of the joints. For the most part,

172. Wheeldon, T.: Some Further Observations of Sulphur Metabolism as Factor in Arthritis—Introduction of Suggestion that Adrenal Function Affects Sulphur Metabolism, *Virginia M. Monthly* **63**:634-636 (Jan.) 1937.

173. Parrish, P. P.; Console, W. A., and Battaglia, J.: Gonococcic Arthritis of Newborn Treated with Sulfanilamide, *J. A. M. A.* **114**:241-242 (Jan. 20) 1940. Culp, O. S., and Cobey, M. C.: Gonorrhoeal Arthritis: Proposed Plan of Sulfanilamide Therapy, *J. Bone & Joint Surg.* **22**:185-199 (Jan.) 1940. Culp, O. S.: Treatment of Gonorrheal Arthritis: Analysis of Two Hundred Cases, *J. Urol.* **43**:737-765 (May) 1940.

174. Hall, M. G.; Bayles, T. B., and Soutter, P.: Vitamin A Requirements in Rheumatoid Arthritis, *New England J. Med.* **223**:92-96 (July 18) 1940.

175. (a) Muether, R. O.: Use of Vitamins in Chronic Arthritis, *J. Missouri M. A.* **37**:111-114 (March) 1940. (b) Wille, E.: Vitamin C and B₁ in Arthritis, *Fortschr. d. Therap.* **16**:118-122 (April) 1940.

176. Snyder, R. G., and Squires, W. H.: Preliminary Report on Activated Ergosterol: Form of High-Dosage Vitamin D in Treatment of Chronic Arthritis, *New York State J. Med.* **40**:708-719 (May 1) 1940.

177. Jacques, R. H.: Relation Between Reduced Ascorbic-Acid Levels of Blood Plasma and Rheumatoid Arthritis, *J. Bone & Joint Surg.* **22**:324-326 (April) 1940.

178. Kahlmeter, G.: *Chronic Rheumatic Diseases*, edited by C. W. Buckley, New York, The Macmillan Company, 1937, p. 17.

179. Smyth, C. J.; Freyberg, R. H., and Peck, W. S.: Experiences with Roentgen Therapy in Various Rheumatic Conditions, *J. A. M. A.* **115**:2209-2210 (Dec. 21) 1940.

patients were selected who had pairs of comparably affected joints, and roentgen treatment was applied to only one of the pair, the untreated joint serving as a control. In still other cases the possible psychic effect of such treatment was studied by screening some joints with lead so that no roentgen rays reached the skin. The effect of such treatment was measured by careful study of the subjective response, observation of physical changes at the joints, frequent determinations of the erythrocyte sedimentation rate, diagnostic roentgen examinations of the joints and noting of changes in synovial fluid from both treated and untreated joints before and after roentgen therapy and in several cases by microscopic study of joint capsule and synovial biopsy tissue.

Results were not encouraging. Rheumatoid arthritis was not improved; spondylitis was most benefited. Pain was relieved, but improvements might be due to psychic effects. Cases were observed for only eighteen months in this series. Holbrook¹⁸⁰ agrees with Freyberg and his co-workers.

Swaim¹⁸⁰ stresses the point that the treatment is local only. The sedimentation rate was therefore not changed in his cases; no changes in the roentgenograms were noted. He believes decrease of pain is the first beneficial result and lessened spasm the second. Since 1932, 164 patients have been treated: 85 with rheumatoid arthritis, 31 with osteoarthritis, 28 with these two forms combined and 18 with Strümpell-Marie arthritis. Swelling decreased, and limited motion improved. Recalcification was observed, as has been reported before. No ill effects have been reported. Ninety per cent of those in whom the swelling and pain in the joints had been of six months' duration or less were improved. Best results are had when treatment is instituted early. Children respond especially well. Frequent small doses continued for a long time give better results than larger doses at longer intervals. Improvement occurs only after a year.

Leddy¹⁸⁰ observes that since arthritis is a chronic inflammatory disease high voltage and large doses are unnecessary. It is worth trial for relief of pain. Freund¹⁸⁰ has had good results. Freiberg (J. A.)¹⁸⁰ is doubtful of the results and feels there is danger due to osteoporosis. Ochsner and Mumford,¹⁸¹ Weinberg,¹⁸² Saralegni¹⁸³ and Jovin¹⁸⁴ report

180. In discussion on Smyth, Freyberg and Peck.¹⁷⁹

181. Ochsner, H. C., and Mumford, E. B.: *Roentgen Therapy for Painful Conditions of Bones and Joints*, Radiology **34**:444-445 (April) 1940.

182. Weinberg, T. B.: *Arthritis and Para-Arthritis Treated with the Roentgen Ray: Report of One Hundred and Sixty-One Cases*, Am. J. Roentgenol. **43**:416-424 (March) 1940.

183. Saralegni, J. A.: *Technique and Results of Deep Radiotherapy in Chronic Rheumatism*, Rev. Asoc. méd. argent. **53**:1095-1097 (Dec. 15) 1939.

184. Jovin, I.: *Limits and Possibilities of Roentgenotherapy in the Treatment of Articular Rheumatism*, Gaz. méd. de France (supp. Cah. radiol.) **47**:122-127 (Jan. 15) 1940.

permanent improvement in both types of arthritis. [ED. NOTE: The best technic apparently has not yet been developed or the treatments controlled enough to give constant results. However, roentgen treatment seems to do no harm and should be investigated further.]

Prevention of Deformity.—The orthopedic surgeon is chiefly responsible for two aspects of the treatment of chronic arthritis, the prevention of deformity and the correction of deformity. The prevention of deformity is possible if the patients are seen early and the joints are adequately splinted. Bell¹⁸⁵ says the importance of prevention of deformity cannot be overemphasized. Splinting is the means recommended; it is easily done and is almost always successful. It should be done early, since deformity once established is most difficult to correct. The fear that immobilization will result in a stiff joint is unfounded; movement aggravates the inflammatory process. Light plaster splints or bivalved casts are to be used as indicated. Atrophic arthritis causes most of the deformities. Persistent flexion causes contractures of the capsule and muscles and results in deformities. This does not happen in hypertrophic joints. Splinting as a form of preventive treatment is now universally recommended. Tippet¹⁸⁶ Stump,¹⁸⁷ Ruiz Moreno and Tarnopolsky,¹⁸⁸ Cecil,¹⁸⁹ Swaim,¹⁹⁰ Haden^{191a} and Hill,^{191b} all advise its use.

Another means of preventing deformity is physical therapy. Correct posture must be stressed. It is necessary for recovery and prevention of further trouble. Krusen¹⁹² stresses three procedures: (1) heat and cold water and electrical measures; (2) mechanical aids, such as massage and manipulation, as well as splinting; (3) exercise, position and rest. He recommends especially rest with the joint in position to prevent

185. Bell, B. T.: Prevention and Correction of Deformities in Arthritis, *M. Clin. North America* **24**:1735-1743 (Nov.) 1940.

186. Tippet, G. O.: Use of Plaster Splintage in Treatment of Arthritis, *Brit. J. Rheumat.* **2**:195-202 (April) 1940.

187. Stump, J. P.: Prevention of Arthritic Deformities by Early Orthopedic Management, *Ann. Int. Med.* **14**:87-99 (July) 1940.

188. Ruiz Moreno, A., and Tarnopolsky, S.: Relation Between Orthopedics and Rheumatism, *Día méd.* **12**:162 (Feb. 26) 1940.

189. Cecil, R. L.: Physical Therapy Compared with Other Measures in Arthritis, *Arch. Phys. Therapy* **21**:581-584 (Oct.) 1940.

190. Swaim, L. T.: Physical Therapy in Arthritis, *Public Health Nursing* **32**:246-247 (April) 1940.

191. (a) Haden, R. L.: Rheumatoid Arthritis: Etiology and Treatment, *Arch. Phys. Therapy* **21**:671-677 (Nov.) 1940. (b) Hill, L. C.: Observations on Treatment of Rheumatoid Arthritis, *Brit. J. Rheumat.* **2**:202-207 (April) 1940.

192. Krusen, F. H.: Physical Treatment of Arthritis, *Arch. Phys. Therapy* **21**:144-153 (March) 1940; Physical Therapy in Arthritis with Special Reference to Home Treatment, *J. A. M. A.* **115**:605-615 (Aug. 24) 1940.

contracture and deformity. Mobilization should be induced by degrees under adequate supervision.

Wyman¹⁹³ recommends under-water exercises in walking. Cecil¹⁸⁹ and Swaim¹⁹⁰ feel that physical therapy is one of the most important measures in the treatment of chronic arthritis but that it should be supervised by a specialist. Martucci¹⁹⁴ describes the physical agents used in the treatment of arthritis, including baking, diathermy, paraffin baths for the hands and feet, mud packs and massage to delay muscle atrophy, restore the tissues, improve the local metabolism, increase circulation and prevent muscle contraction. Hydrotherapy, exercise and rest are also mentioned. Massage, active and passive exercises and muscle training in posture correction are most important¹⁹⁵ and should be followed by occupational therapy, which is of great value physically as well as mentally. Home work should be planned,¹⁹⁶ as it is vitally important to maintain the morale.

Correction of Deformity.—The correction of deformity can be accomplished by slow manipulation and frequent changes of casts as the relaxation takes place. Frequently, however, a reconstructive operation is necessary both for rheumatoid arthritis and for hypertrophic hips.¹⁹⁷ Bell¹⁸⁵ states that when the joint has been quiescent for from three to six months operation may be used to correct deformities after the muscles have been strengthened. Manipulation, active exercises and splints are

193. Wyman, J. F.: Advantages of Institutional Care and Physical Therapy in Chronic Arthritis, *Arch. Phys. Therapy*. **21**:301-304 (May) 1940.

194. Martucci, A. A.: Physical Therapy in the Treatment of Chronic Arthritis, *M. Clin. North America* **24**:1685-1696 (Nov.) 1940.

195. Kullberg, R. W., and Lowell, L. M.: The Physiological Approach to Rheumatoid Arthritis, *Rocky Mountain M. J.* **37**:114-116 (Feb.) 1940. Kendrick, J. I.: Physical Therapy Principles of Peri-Arthritis of the Shoulder, *Arch. Phys. Therapy* **21**:41-44 (Jan.) 1940. Hamilton, J. F.: Use and Misuse of Physical Therapeutics in Treatment of Arthritis, *Memphis M. J.* **15**:184-187 (Nov.) 1940.

Frazier, V. E.: Underwater Therapy in Chronic Arthritis, *J. Missouri M. A.* **37**:192-193 (May) 1940. Kahlmeter, G.: Treatment of Arthrosis and Spondylosis with Therapeutic Gymnastics, *Nord. med. (Hygiea)* **5**:343-346 (Feb. 24) 1940.

Hummel, R.: Therapeutic Exercises with Elimination of Pain by the Intravenous Strontium Bromide Injections and Contribution to Roentgenotherapy, *Med. Welt* **13**:1533-1534 (Dec. 2) 1939. Fletcher, G. B.: Underwater or Pool Treatment of Certain Conditions of Muscles, Nerves and Joints, *Tri-State M. J.* **12**:2411 (Jan.) 1940. Sherwood, K. K.: Physical Therapy in Arthritis, *Physiotherapy Rev.* **20**:134-137 (May-June) 1940.

196. Bell, C., and Swaim, L. T.: Occupational Therapy in Arthritis, *Pub. Health Nursing* **32**:243-245 (April) 1940. Pattee, G.: Prescribed Exercises to Be Carried Out at Home: Home Occupational Therapy, *Occup. Therapy* **19**:169-175 (June) 1940. Elliston, W. A.; Silber, M. F., and Grover, D.: Physiotherapy in Rheumatoid Arthritis, *New England J. Med.* **224**:150-156 (Jan. 23) 1941.

197. Charry, V.: Role of the Practitioner in Orthopedic and Surgical Therapy of Chronic Rheumatism, *Monde méd.* **49**:828-831 (Nov.) 1939.

effective when the condition is mild. Manipulation with the patient under an anesthetic may be used but is dangerous in cases of rheumatoid arthritis. Wedge casts are good for correcting deformities of the joints of extremities. Lengthening of the tendons and capsulotomy are of value when the knee is subluxated. Removal of the synovial membrane is a valuable procedure when there is chronic hypertrophic synovitis. Resection of the patella is performed when movement of the patella is limited. Cheilotomy helps when osteophytes form a block to movement. Arthroplasty is of value in cases of ankylosis of the hip, knee or elbow. When only one weight-bearing joint is badly damaged, arthrodesis is satisfactory, as it produces a painless, stable extremity. Osteotomy is valuable in correcting bony ankylosis in a deformed position.

Pfeiffer and Bach¹⁹⁸ feel that all patients must be thoroughly studied and the essential medical measures carried out. Splinting and corrective and muscle-setting exercises must be used prior to surgical intervention. Operation is best only after the disease has been inactive for at least a year. Synovectomy is used when the usual supportive measures have not been satisfactory and the persistent pathologic changes are confined to the synovia. It restores the range of motion to from 90 degrees to normal, depending on the case, and makes walking possible. Posterior capsuloplasty may be used when there is little damage to the cartilage. Sometimes a combination of the two operations is recommended. The follow-up by surgeon and internist is important.

Ghormley and Cameron¹⁹⁹ report 103 synovectomies in 88 patients, 14 bilateral. The operation is best adapted to the knee joint. Of 90 cases with synovitis, in 34.4 per cent the result was excellent, in 33.3 per cent there was improvement, and in 32.2 per cent the result was poor.

All patients with traumatic arthritis, osteochondromatosis, xanthoma and hypertrophic arthritis were cured or improved. Of the patients with chronic synovitis, 77.4 per cent were cured or improved; of those with chronic infectious arthritis, 56.2 per cent, and of those with synovitis which later developed into chronic infectious arthritis, 54.9 per cent. In discussing this, Swett²⁰⁰ shows that in 24 of 52 cases of atrophic arthritis there was improvement or an excellent result. His figure agrees with the contention of Inges that synovectomy offers 50 per cent improvement to one-half the patients with atrophic arthritis. He feels that the

198. Pfeiffer, D. B., and Bach, T. F.: *Reconstructive Surgery in Chronic Rheumatoid Arthritis*, M. Clin. North America **24**:1745-1753 (Nov.) 1940.

199. Ghormley, R. K., and Cameron, D. M.: *The End Results of Synovectomy of the Knee Joint*, J. A. M. A. **115**:2208-2209 (Dec. 21) 1940.

200. In discussion on Ghormley and Cameron.¹⁹⁹

conditions under which synovectomy can be expected to yield a high percentage of good results depend on the type of disease and the stage of the process. One must remember that the operation is applicable only to (1) a synovial proliferative process, (2) increase of the perichondrium, endosteum and epiphysial connective tissue and (3) sites where capsular fibrous or muscular fibrous tissue is predominant. Therefore, patients with synovial involvement must be operated on as soon as proliferation is found not to undergo spontaneous resolution before it has caused damage to the structure of the joint, and before protracted invalidism has caused depletion.

Failures are due to the fact that operation is performed in cases of other than synovial involvement or to tardiness in operating. Dickson,²⁰⁰ reporting on 140 synovectomies, says that proper removal of synovia and other material from an infected joint results in improvement in other joints in a large percentage of cases. It cannot be ignored that failures are traceable to incomplete operation. Disintegrated semilunar cartilages, all destroyed cartilages, all hypertrophic osteophytes, all pannus and projecting hypertrophic margins must be removed to obtain good results.

Key²⁰⁰ agrees that radical synovectomy should be done early in cases of presumable rheumatoid arthritis. Ghormley¹⁹⁹ believes that it is most important to select the cases and perform radical operations and later manipulate for three or four weeks.

Henderson and Pollock²⁰¹ report 77 cases of osteoarthritis of the hip joint. Men predominated over women among the patients, 55 to 22. The authors state: "From the point of view of therapy, undoubtedly, arthrodesis as performed by us has given the best results, but, while this is a procedure which is readily accepted in Europe, in America we have difficulty in convincing our patients of the benefits to be derived from a stiff hip. . . . Of the other procedures, each has its place in well-selected cases. Drilling, combined with manipulative measures and followed by active movements, aided by physical therapeutic agents, has given good results in many cases. The more recent work of Smith-Petersen with vitallium caps in arthroplasty of the hip joint bids fair to change our views on this operation, but, until further experience has been gained, the procedure is still *sub judice*." Acetabuloplasty and extensive cheilotomy give excellent results in some cases.

Lewis and Graham²⁰² stress the importance of extreme care in handling fractures of the ankle because of the secondary osteoarthritis which may result and is crippling.

(To Be Continued)

201. Henderson, M. S., and Pollock, G. A.: Surgical Treatment of Osteoarthritis of Hip Joint, *J. Bone & Joint Surg.* 22:923-931 (Oct.) 1940.

202. Lewis, R. W., and Graham, W. C.: Secondary Osteoarthritis Following Fractures of the Ankle, *Am. J. Surg.* 49:210-218, (Aug.) 1940.

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OSTEOGENIC SARCOMA

AN ANALYSIS OF EIGHTY CASES

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Osteogenic sarcoma is the most common type of primary malignant tumor of bone. In the American Registry of Bone Tumors it is represented by the largest number of reported cases, namely, 1,071 out of a total of 2,232 cases. Mercer¹ estimated its incidence as 1 in 75,000 of the general population. At the University Hospital during the period from 1925 to 1938, inclusive, this diagnosis has been established in 80 of 305,760 consecutive hospital registrations, an incidence of 1 to approximately 3,800 registrations. It is believed that osteogenic sarcoma was seen in more cases during this period, but in the additional cases the criteria for diagnosis were not sufficiently well established to warrant inclusion of these cases in this series.

GENERAL CONSIDERATIONS

Osteogenic sarcoma is primarily a disease of the young. In 40 of our cases, or 50 per cent, it occurred in the second decade of life. The average age of the patients at the time of admission was 29 years; the youngest was 8 years of age; the oldest was 72. Figure 1 shows the distribution of the tumors in our series according to decades of life.

The sex incidence was 51 men and 39 women, or 64 and 36 per cent, respectively.

The family history was positive for one or another type of tumor in 11 cases, or 13 per cent. There was no family history of tumor in 51 cases, and in the remainder this fact was not ascertained.

Twenty-nine patients, or 36 per cent, gave a history of trauma preceding the onset of symptoms. The trauma was usually not severe

From the Department of Surgery, Section of Orthopedics, University of Michigan Medical School.

1. Mercer, W.: *Orthopaedic Surgery*, ed. 2, Baltimore, William Wood & Company, 1936.

and on the average antedated the symptoms by a few weeks to a few months. The high proportion of patients with a history of trauma has been noted repeatedly in the literature and suggests that trauma may play an etiologic role in the development of osteogenic sarcoma.

The average duration of symptoms from the onset until the time of admission was thirteen months. The shortest duration was in a patient who had noted a painless swelling over the maxilla two weeks previous to admission. The longest duration of symptoms was ten years; a diagnosis of an osteochondroma with malignant change was made in this

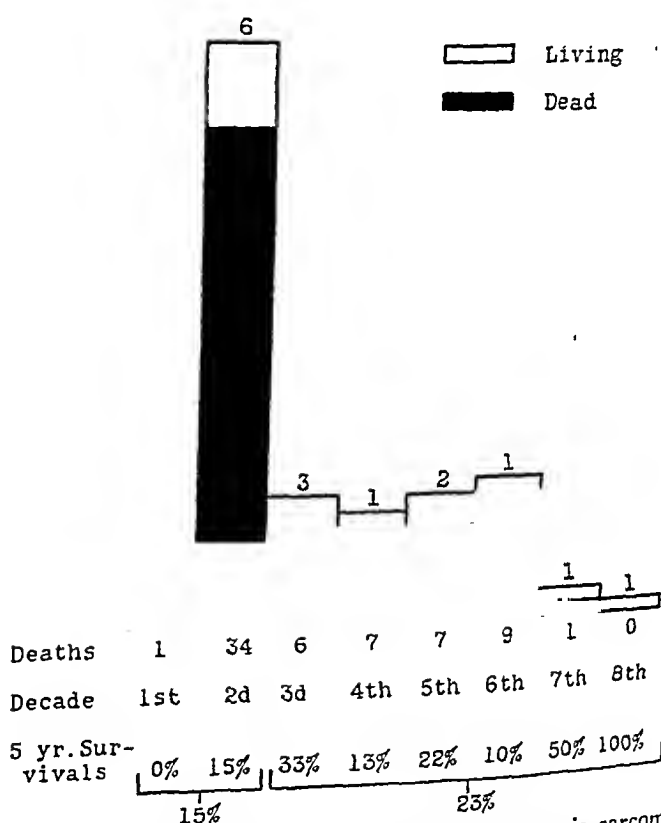


Fig. 1.—Distribution of the tumors diagnosed as osteogenic sarcoma according to decades of life, with the number of patients in each age group who have died, the number who are living, and the percentage of five year survivals.

patient, and it is probable that the malignant process had not been present during the entire period of symptoms.

The outstanding symptoms were pain and swelling. Pain was present in all but 1 patient. The pain almost invariably preceded the appearance of the tumefaction. This is of some significance, since in many benign tumors of bone, pain, if it is present, is noted after the appearance of the swelling. The pain in most instances was relatively mild at the onset, rapidly becoming more constant and severe. It was often worse at night. When well developed, the pain was not relieved by rest. It was followed after a variable period by swelling of the involved area. Motion of the adjacent joint then became affected, and

a limp developed in the lower extremity. Many patients were unable to walk without external support at the time of admission. Constitutional manifestations, such as fever, loss of weight, anorexia and ready fatigue, were noted in a relatively small proportion of the cases. Almost without exception the patients were in good general health at the time of the onset of symptoms.

A palpable tumor was present in 73 cases, or 91 per cent. The tumor was hard in consistency and usually moderately tender. Increased heat

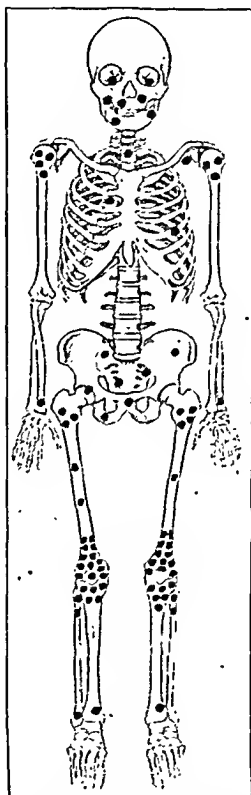


Fig. 2.—Distribution of lesions, showing predilection for the ends of long bones.

and dilatation of the superficial vessels over the tumor were frequently noted. In the extremities there was limitation of motion of the adjacent joints. Ulceration of the overlying skin was noted in 5 cases, although this is generally considered an unusual finding. Regional lymphadenopathy was noted in only 2 cases. The patient's general condition was usually good on admission though a low grade fever was an occasional finding.

In this series the lesions showed a marked predilection for the ends of the long bones. In 40 cases, or 50 per cent, they were located

in the vicinity of the knee joint as follows: lower end of the femur in 25 cases; upper end of the tibia in 11 cases; upper end of the fibula in 4 cases. Figure 2 shows the distribution of the lesions.

In this series the diagnosis was established on the basis of the combined clinical, roentgenologic and histologic studies in 62 cases. In the remaining 18 cases, histologic examination was not carried out, but there were typical clinical and roentgenologic findings, with the appearance of metastases, followed by death within a relatively short time.

The classification of tumors of this type into subgroups is beset with many difficulties, and unanimity among various examiners of the same lesions is unusual. However, an attempt was made to classify the tumors in this series according to the criteria outlined by Geschickter and Copeland² into the following groups: (1) primary myxochondrosarcoma, (2) secondary chondrosarcoma, (3) osteoblastic (sclerosing)

TABLE 1.—*Correlation Between the Types of Osteogenic Sarcoma and the Periods of Survival in 48 Cases*

Type of Lesion	Cases	Average Period of Survival, Mo.	Five Year Survivals	Percentage of 5 Yr. Survivals
Primary myxochondrosarcoma.....	11	13	1	9
Secondary chondrosarcoma.....	14	33	4	29
Sclerosing osteogenic sarcoma.....	14	48	6	43
Chondroblastic sarcoma.....	2	16	0	0
Osteolytic osteogenic sarcoma.....	7	10	0	0

osteogenic sarcoma, (4) chondroblastic sarcoma and (5) osteolytic sarcoma. Of the 62 tumors from which material was available for histologic study, it was believed that 48 allowed fairly accurate classification into these subgroups. Table 1 shows the classification of these 48 lesions.

The treatment of choice in this series was radical amputation. This was usually carried out without preoperative application of roentgen radiation. When used postoperatively, roentgen therapy was employed as a palliative measure, generally for pulmonary metastases. Local excision was carried out for lesions in locations not amenable to amputation, usually with postoperative roentgen therapy. In a few cases roentgen therapy only was used, in each instance as a palliative measure for far advanced lesions. Three patients received symptomatic treatment only. Table 2 shows the types of treatment employed and the number of cases in each group.

END RESULTS

Follow-up studies were carried out in every case in this series. Sixty-three patients died, a mortality rate of 79 per cent. Of the 17

2. Geschickter, C. F., and Copeland, M. D.: Tumors of Bone. New York, American Journal of Cancer, 1936.

patients who survived, 1 patient had metastases, and the others were well at the time of writing. The shortest period of survival was that of a patient who died within twenty-four hours after resection of a lesion involving the ribs. The longest period of survival was that of a patient who was still living and well fourteen years and seven months after a midhigh amputation. The average period of survival in cases with a fatal termination was thirty-one months. The average period of survival of those who were living at the time of the last follow-up study was eighty-four months. The average period of survival for the entire eighty cases at the time of writing was forty-one months. There were 15 5-year survivals, an incidence of 19 per cent. There were 4 ten year survivals. The discrepancy between the numbers of five and ten year survivals is explained by the fact that only 4 patients have had a ten year follow-up study. That even a ten year survival

TABLE 2.—*Correlation Between the Types of Treatment and the Periods of Survival in 80 Cases*

Type of Treatment	Cases	Average Period of Survival, Mo.	Five Year Survivals	Percentage of 5 Yr. Survivals
Amputation.....	22	35	6	27
Amputation and roentgen therapy.....	21	43	7	33
Local excision.....	3	22	1	33
Excision and roentgen therapy only.....	10	21	1	10
Roentgen therapy only.....	20	7	0	0
Symptomatic.....	3	25	0	0

does not constitute a cure is shown by the fact that 1 patient died of pulmonary metastases which developed thirteen years after a midhigh amputation.

PROGNOSIS

Many factors influence the prognosis of a patient with osteogenic sarcoma. To evaluate these factors an attempt was made to correlate the period of survival with the age of the patient, the duration of symptoms previous to treatment, the status of the neoplasm on admission, the performance of biopsy before or at the time of treatment, the location of the lesion, the type of the lesion and, finally, the type of treatment, including the site of amputation.

The average period of survival following treatment for the entire series was twenty-nine months. Forty-one patients were below 20 years of age; in this group the average period of survival was twenty-one months, and there were 6 five year survivals, or 15 per cent. Among the 39 patients aged 20 years and above, the average period of survival was thirty-five months, and there were 9 five-year survivals, or 23 per cent. Thus, in the older group the prognosis was considerably better both with regard to the average period of survival

and the percentage of five-year survivals. The 2 oldest patients, aged 69 and 72 years, were living and well, eighty-three and sixty-six months, respectively, after treatment.

Ferguson,³ in a recent review of 400 cases of osteogenic sarcoma, compared the prognosis for patients who received treatment less than six months after the onset of symptoms with the prognosis for patients who received treatment more than six months after the onset of symptoms. It was found that the group with the greater duration of symptoms had the better prognosis. In this series 46 patients had symptoms less than six months; among these the average period of survival was twenty months, and there were 8 five year survivals, or 17 per cent. Among the 34 patients having symptoms more than six months the average period of survival was thirty-one months, and there were 7 five year survivals, or 23 per cent. These figures are in agreement with those of Ferguson. It is believed that the explanation of this apparent indication for the delay of treatment lies in the fact that the more malignant type of lesion drives the patient to seek aid earlier in the course of his disease.

The average period of survival of those patients who had metastases on admission was only four months as compared with an average of twenty-nine months for the entire series.

There were 19 patients who underwent biopsy previous to surgical treatment. The biopsy was usually carried out a few days previous to the subsequent procedure. The average period of survival in this group was twenty-eight months, compared with an average of thirty-five months for the group which did not have previous biopsy. The danger of a preliminary biopsy has never been conclusively demonstrated, and the evidence herewith produced is regarded as merely suggestive.

The correlation between the sites of the lesions and the periods of survival is shown in table 3. As might have been expected, the group with the more central lesions had a shorter average period of survival and fewer five year survivals. This fact is strikingly illustrated by comparing the periods of survival of two groups of patients, those with lesions above and those with lesions below the knee. The average period of survival and the number of five year survivals were more than twice as favorable in the group with lesions below the knee.

It is obvious that the most important factor in determining the prognosis in any patient is the type of lesion. If all patients with osteogenic sarcoma had approximately the same prognosis, the classification of the lesions into various subgroups would have little more

3. Ferguson, A. B.: Treatment of Osteogenic Sarcoma, *J. Bone & Joint Surg.* **22**:92-96 (Jan.) 1940.

than academic value. However, an analysis of 48 cases showed considerable variation in prognosis between the various types, as shown in table 1. Progressing from the least favorable to the most favorable prognosis, the order was found to be osteolytic osteogenic sarcoma, chondroblastic sarcoma, primary myxochondrosarcoma, secondary chondrosarcoma and sclerosing osteogenic sarcoma. These results agree in general with those recorded by Geschickter and Copeland² and furnish another demonstration of the fact that the more highly differentiated the lesion the better the prognosis.

Table 2 shows the results of the various types of treatment employed. All but 2 of the patients with five year survivals underwent amputation, either with or without roentgen therapy. For the 43 patients treated by amputation, the average period of survival was forty-two months, and there were 13 five year survivals, an incidence of 30 per cent. This was in striking contrast to the results in 37 patients

TABLE 3.—*Correlation Between the Sites of Osteogenic Sarcoma and the Periods of Survival in 80 Cases*

Site of Lesion	Cases	Average Period of Survival, Mo.	Five Year Survivals	Percentage of 5 Yr. Survivals
Trunk.....	11	21	1	9
Face and skull.....	7	25	1	14
Upper extremity.....	9	27	2	22
Lower extremity.....	63	30	11	21
(a) Above knee.....	35	21	5	14
(b) Below knee.....	18	49	6	33

not treated by amputation, for whom the average period of survival was fifteen months and the number of five year survivals only 2, an incidence of 5 per cent. It would seem that amputation still offers the best chance of cure of osteogenic sarcoma. The results in the patients treated by amputation plus roentgen therapy were a little more favorable than those in patients treated by amputation alone. However, roentgen therapy was almost always used for palliation of pulmonary metastases, and no conclusions regarding the curative value of roentgen therapy in cases of osteogenic sarcoma are warranted from a study of this series.

It has been stated that amputation should be carried out at the next higher joint, at least, and never through the bone involved. In this connection it is interesting to compare the results of amputation through a thigh for a lesion below the knee with the results of amputation through a thigh or disarticulation of a hip for a lesion above the knee. In only 1 case was it considered justifiable to amputate below the knee; the patient had a lesion of the distal part of the tibia and is living and well at the time of writing, seventy months after

treatment. Thirteen patients underwent a thigh amputation for a lesion below the knee; in this group the five year survivals numbered 5, an incidence of 38 per cent. Sixteen patients with a lesion of the femur were treated by a midthigh or high thigh amputation; in this group five year survivals numbered 5, an incidence of 31 per cent. Thus, including the patient who underwent amputation through the tibia, there were 17 patients in whom the involved bone was transected, with 6 five year survivals, an incidence of 35 per cent. Disarticulation of a hip was carried out in 8 patients with a lesion of the femur, and in this group there were no five year survivals. Thus, there were 21 patients in whom amputation was carried out proximal to the involved bone, with five year survival in 5, an incidence of 28 per cent. Table 4 shows the correlations.

It is evident, as Coley and Pool⁴ have pointed out, that the dictum that amputation should be carried out at the next higher joint,

TABLE 4.—*Correlation Between the Sites of the Lesions, the Levels of Amputation and the Periods of Survival in 38 Cases*

Site of Lesion	Site of Amputation	Cases	Average Period of Survival (Mo.)	Five Year Survivals	Percentage of 5 Yr. Survivals
Tibia or fibula.....	Upper part of tibia.....	1	70	1	100
	Lower part or middle of thigh	13	53	5	38
Femur.....	Middle or upper part of thigh	16	37	5	31
	Disarticulation of hip.....	8	11	0	0

at least, and never through the involved bone is without support. Death, if it occurs, is almost always due to distant pulmonary metastases, and, as has been previously noted, the more centrally located the lesion the poorer the prognosis. This is a sufficient explanation for the poor results of disarticulation of a hip. It is believed that for any lesion in an extremity the lowest level of amputation compatible with complete eradication and the requirements for a suitable prosthesis should be considered satisfactory.

In this series there were 4 patients who had recurrence in the stump. In 2 patients there was recurrence after disarticulation of a hip. For these patients hemipelvectomy was not considered justifiable. 1 had involvement of the neck of a femur, and the other had involvement of the subtrochanteric area of a femur. There was 1 patient who had a recurrence after amputation in the upper part of the thigh for a lesion extending 8 inches (20 cm.) above the knee joint. Perhaps disarticu-

4. Coley, B. L., and Pool, J. L.: Factors Influencing Prognosis in Osteogenic Sarcoma, *Ann. Surg.* **112**:1114-1128 (Dec.) 1940.

lation of the hip was indicated in this patient, but in our series there were no five year survivals after such treatment. There was 1 patient who had a recurrence in the stump following amputation in the lower part of the thigh for a sarcoma of the upper part of the tibia; undoubtedly a higher level of amputation was indicated, but in this patient the usual rule was violated, that osteogenic sarcoma does not "jump a joint."

The progressive encouragement to which a patient is entitled as he outlives his lesion after treatment suggested the computation of the odds on a cure at the end of each successive year of survival. The results are shown in table 5. Seventy-six patients have either died or survived treatment more than five years without evidence of recurrence or metastases. Since 2 of the 15 patients with five year survivals died as a result of the extension of their malignant lesions, only 13

TABLE 5.—Odds on Survival at Different Periods of Survival*

Interval of Time	Pat.ents Dead	Patients Living	Percentage of Cures	Odds on Cure
Admission.....	0	76	17	1 to 5
End of first year.....	43	33	39	2 to 3
End of second year.....	9	24	54	5 to 4
End of third year.....	7	17	76	3 to 1
End of fourth year.....	2	15	87	7 to 1
End of fifth year.....	0	15	87	7 to 1
After fifteen years.....	2	13	100	100%

* The calculations are based on 76 cases with 13 cures; 2 patients died after survival period of five years.

patients are regarded as having been cured. At the time of admission the patient's chance of a cure was 1 to 5, whereas at the end of the fifth year it was 7 to 1. Judging from the patient who died of his lesion more than thirteen years after treatment, one cannot absolutely rule out the likelihood of recurrence after the lapse of at least that many years.

SUMMARY AND CONCLUSIONS

Osteogenic sarcoma is the most common type of primary malignant tumor of bone. It is primarily a disease of the young, one half of the patients being in the second decade of life. It is more common in men than in women. Only a small proportion of the patients have a family history of one or another type of malignant lesion. Trauma is associated with the development of osteogenic sarcoma in about one third of the patients.

The average duration of symptoms from the onset until diagnosis is thirteen months. The outstanding symptom is pain followed by swelling. A palpable tumor is present in 90 per cent of cases. The lesions show a marked predilection for the ends of the long bones; about 50 per cent of the lesions appear in the vicinity of the knee

joint. The diagnosis is based on a combination of characteristic clinical findings and roentgenographic and histologic observations. The treatment of choice is primary amputation. If the lesion is not amenable to amputation, local excision should be carried out in conjunction with roentgen therapy.

In this series there was a mortality rate of 79 per cent at the time of writing. The average period of survival was forty-one months. Among 80 patients there were 15 five year survivals, an incidence of 19 per cent. There were 4 ten year survivals, an incidence of 5 per cent. The longest period of survival was that of a patient who was living and well fourteen years and seven months after treatment. One patient died of pulmonary metastases which developed thirteen years after a midthigh amputation.

The prognosis is more favorable for patients over 20 years of age. The prognosis is less favorable for patients with a relatively short duration of symptoms when the diagnosis is established; for the more lethal lesions drive the patients to seek earlier treatment. The danger of the dissemination of tumor cells by a preliminary biopsy has not been conclusively demonstrated. In the extremities, the more central the lesion the poorer the prognosis. The prognosis varies directly as the degree of differentiation of the lesion. If the lesion occurs in an extremity, the period of survival is most favorably influenced by amputation. Transection of the involved bone is not contraindicated, provided it is above the upper limits of the lesion. As the patient outlives his lesion after curative therapy, the prognosis becomes progressively more favorable.

REPRODUCTION OF ULCERATIVE COLITIS IN DOGS

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The attempt to reproduce ulcerative colitis in dogs was prompted by the work of Reichert and Mathes,¹ who experimentally produced lymphedema of the intestinal tract. Similarity was noted between experimental lymphedema and clinical regional enteritis or terminal ileitis. The extension of ulcerative colitis into the small intestine as ileitis has been recognized in certain cases.

This experimental work followed a procedure for producing obstruction of the mesenteric lymphatics by the injection of a sclerosing solution which has been described elsewhere.¹ An attempt was made to inject the solution into the lymphatics draining the terminal portion of the ileum and the colon in order to produce the disease process primarily in the colon rather than in the ileum. Preliminary injections of several types of bacteria were made in an effort to determine which is most pathogenic for the colon and produces the most marked disease process in that organ.

METHOD

The sclerosing solution used was the one which Reichert and Mathes found most satisfactory, namely, a 26 per cent bismuth oxychloride aqueous solution to which a small amount of rose aniline dye (in the form of indelible lead) was added. The bismuth oxychloride solution was prepared according to Poth's² modification of Hill's bismuth oxychloride mass (1 part of bismuth to 2 parts of oxychloride powder). This was injected into one or more lymphatics in small amounts, close to the intestine. A fat meal given three to four hours before operation was the most satisfactory means of dilating the lymphatics for injection. The sclerosing solution could not be injected directly into the lymphatics in the mesocolon proper owing to the lack of dilatation of these lacteals by the ingested fat; dilation decreased progressively toward the distal end of the intestinal tract. Therefore the injection was made as close to the colon as possible in the mesentery of the ileum. The injections were made through a short-beveled

Prof. Samuel C. Harvey and Asst. Prof. Gustaf E. Lindskog assisted in carrying out the experiments.

1. Reichert, F. L., and Mathes, M. E.: Experimental Lymphedema of the Intestinal Tract and Its Relation to Regional Cicatrizing Enteritis, *Ann. Surg.* 104:601 (Oct.) 1936.

2. Poth, E. J.: A Modification of Hill's Radiopaque Mass for the Injection of Lumina, *J. Lab. & Clin. Med.* 19:1241 (Aug.) 1934.

gage 27 hypodermic needle; a magnifying dissecting loupe was used to accentuate the lumens of the tiny vessels, as described by Homans, Drinker and Fields.³ A sufficiently large amount of solution was injected to fill partially the nodes at the base of the mesentery, thereby obstructing the lymphatic drainage from the colon as well as from the terminal portion of the ileum. A twenty-four hour broth culture of living organisms was injected intravenously into some of the animals three hours before operation. Saline washings of organisms from a blood agar slant culture were used in some experiments without any noticeable difference in reaction. In 1 case the living organisms were mixed with the sclerosing solution and injected directly into the lymphatics at operation.



Fig. 1.—Roentgenogram showing radiopaque material in the mesenteric lymphatic vessels and a lymph node.

Cultures of *Bacillus coli*, *Streptococcus viridans*, *Staphylococcus aureus* and *Streptococcus haemolyticus* were used individually in 1 or more instances. All the dogs except 1 were maintained until spontaneous death in an effort to observe results over a long postoperative period. Infusions of saline and dextrose solution were used in a number of the animals to prolong their postoperative course.

The postoperative symptoms in all of these dogs were about the same for the first several weeks. All of them lost any desire for the usual dog diet and would take only small amounts of water and ground meat. On about the second

3. Drinker, C. K.; Fields, M. E., and Homans, J.: The Experimental Production of Edema and Elephantiasis as a Result of Lymphatic Obstruction. *Am. J. Physiol.* 108:509 (June) 1934.

postoperative day profuse bloody diarrhea, often amounting to several pints of almost gross blood, developed in all the dogs. During this period they showed a rapid loss of strength and activity. Some of them vomited bloody material for several days preceding death. The actual cause of death in a number of these animals was shock from the loss of blood by hemorrhage into the intestine.

The 3 animals which lived longer than two weeks gradually regained some of their appetite and activity but lost weight and strength until they died. Moderate diarrhea persisted in these animals, although the bleeding stopped. Dog 1 lost one third of its original body weight in five months. Dogs 2 and 3 each lost one fifth of their original weight in two and four months, respectively. Large ulcers developed on the hindlegs of dog 3; these progressed in size until the dog died.

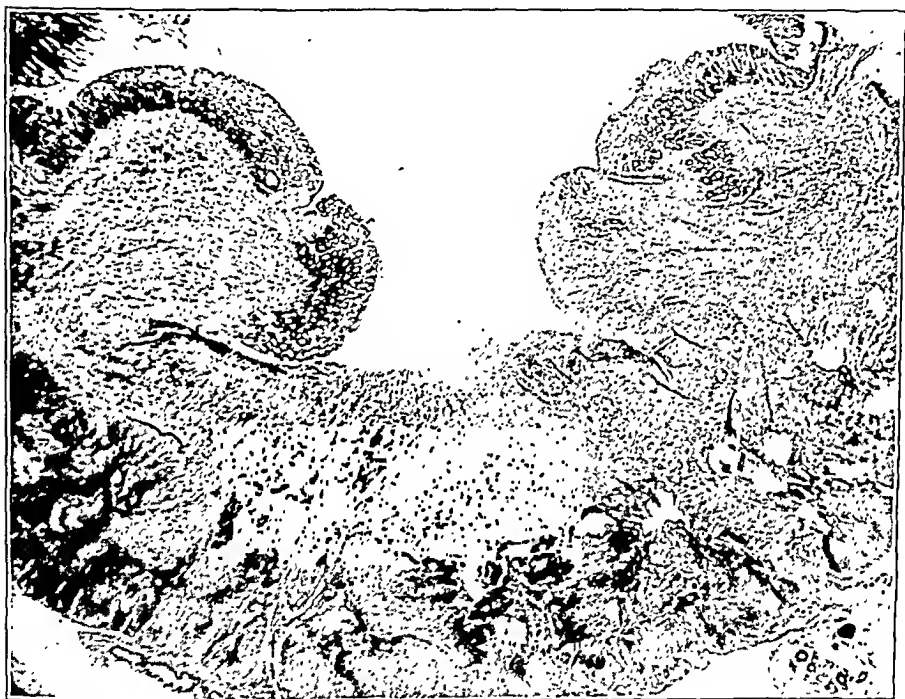


Fig. 2.—Section of colon taken from dog 2 showing deep ulceration of the mucosa with a cellular infiltration extending down into the deep muscular layers. This dog received no bacterial injection and lived two months after operation.

Autopsy was performed as soon as possible in every case, with immediate fixation of the intestines in solution of formaldehyde U. S. P. to prevent autolysis.

RESULTS

The common pathologic finding in all the intestines was marked enlargement of the lymph nodes draining the injected portions of the intestines. This enlargement of the lymph nodes appeared generalized in a number of cases, including all the nodes at the base of the mesentery. These nodes were firm and showed large amounts of foreign material, some of which was present in large phagocytes. Extensive calcium

deposits and fibrosis were noted in the mesenteric nodes of dog 1, which lived for five months after operation. The mesentery of the injected portions of bowel was much thickened and shortened with numerous adhesions in dogs with the more chronic involvement. The walls of the

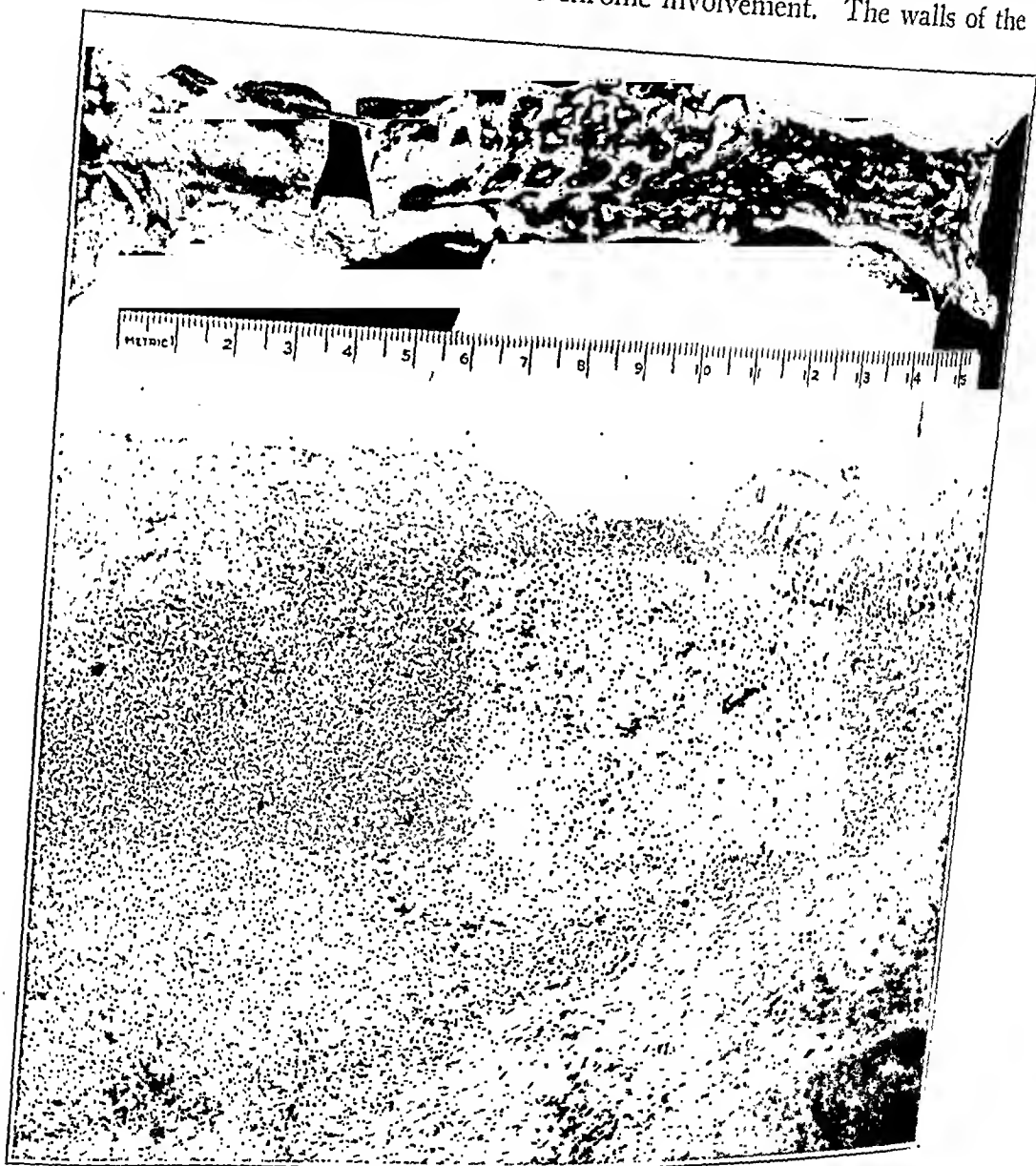


Fig. 3.—The gross and microscopic pictures of an extensive area of ulceration of the colon, with complete destruction of the mucosal layer and a heavy cellular infiltration of the wall in this area.

injected intestinal segments in the animals which lived longer than two weeks were all somewhat thickened, and the lumens were narrowed. The walls of the involved ileum in some of the animals with acute, short-term involvement appeared thin, friable and about ready to rupture. Actual acute and chronic ulceration of the mucosal layer of the colon was noted in 5 animals (2, 8, 13, 14 and 15). Only 1 of these animals

(2) had received any bacterial injection. No ulceration was noted in the ileum of any animal, although the wall of the ileum was definitely involved in the disease process in all of them.

Microscopic examination of the mesenteric lymph nodes and vessels showed marked variation depending on the stage of the disease process when death occurred. In animals with the acute form of the disease the mesenteric lymphatic vessels were crowded with large accumulations of polymorphonuclear and mononuclear cells and phagocytes containing foreign pigment. The long term dogs showed obliteration of the lumens



Fig. 4.—Section taken from the edge of a beginning ulceration of the mucosa of the colon in dog 14 showing cellular infiltration in the mucosal and submucosal layers and irregularity of the mucosal patterns. This animal was killed on the tenth day after operation, at an acute stage of the experimental disease.

of the lymphatic vessels by organizing thrombi and fibrosis. The same fibrotic reaction around the foreign pigment often replaced a large part of the lymphoid tissue in the mesenteric lymph nodes. No thrombosis, either gross or microscopic, was noted in any of the blood vessels in the mesentery proper.

The histologic examination of the intestine showed a moderate to marked cellular reaction in the submucosal layer of the injected segment, gradually fading out in the adjoining segments. This cellular reaction varied from a single layer of cells to a heavy infiltration of the submucosal region with marked hyperplasia of the lymph follicles. This cellular



Fig. 5.—The gross and microscopic pictures of an area of early ulceration of the mucosa of the colon of dog 15 showing marked thickening of the submucosal layer associated with extensive cellular infiltration.

proliferation was most marked in the animals with the acute form of the disease, especially around the actual ulcerations of the mucosa of the colon. In these areas the intestinal wall was increased to three or more times normal thickness as measured against uninvolved portions of the same bowel. Part of this cellular response in the chronic form was replaced by increased fibrous tissue in the submucosal region, although this cellular proliferation was present to a certain degree in both the small and the large bowel in both the acute and the chronic involvements.

The ulcerations found in the mucosa of the colon were frequently extensive. They were almost always found in the most proximal portions of the large bowel, which was the area receiving the major portion of the injections. The ulcerations varied greatly in depth, ranging from destruction of the mucosal layer alone with preservation of the muscularis mucosa to deep ulceration extending down into the deep muscle layers of the wall. The bases of these ulcers were lined by both polymorphonuclear and mononuclear cells and showed thrombi in the smaller-sized vessels. An apparently healing ulceration was seen in the mucosa of the colon of one of the long term dogs (1). This ulceration was distinguished by a disruption of the mucosal pattern over certain areas of thickened wall, accompanied by the presence of glandular structures in the submucosal region.

The pathologic reaction in the small intestine was different in that marked edema and loss of the mucosa covering the tips of the folds occurred rather than ulceration as in the colon. The underlying submucosal cellular reaction appeared to extend right into the tips of the villi in the acute forms. This enteritis was the probable cause of the severe hemorrhages into the bowel during the acute stages.

COMMENT

The results in 6 of the 21 dogs given injections were discarded owing to technical difficulties which caused the death of the animals during the first few postoperative hours, such as too large injections of sclerosing solution or pulmonary congestion after vomiting and aspiration of the fatty meal. Consideration of the remaining 15 animals reveals the following types of preparation: 11 animals had intravenous injections of bacteria before operation (4 of these were given *Str. viridans* [5, 8, 10 and 12], 3 were given *Staph. aureus* [4, 6 and 9], 2 were given *Str. haemolyticus* [7 and 11], and 1 was given *B. coli* [1]); 1 dog (3) was given *B. coli* mixed with the sclerosing solution, injected directly into the mesenteric lymphatics at operation; 4 animals (2, 13, 14 and 15) received no bacterial injections.

The postoperative survival period varied for the 15 dogs; 3 (1, 2 and 3) lived longer than two weeks, and only an additional 2 (7 and 14) lived longer than eight days.

All these 15 animals had a pathologic response in the region of the injected mesentery, ranging from acute enteritis to ulceration and fibrosis of the intestinal wall. Only 1 animal (2) that received a bacterial injection presented ulceration of the mucosa of the colon. All of the animals which did not receive intravenous bacterial injections showed actual ulceration of the mucosa. The apparent reason for this was that a more localized and chronic type of inflammation was induced in the intestinal walls of these animals by the bacteria which were naturally present, in contrast to the overwhelming enteritis produced by the injections of organisms into the blood stream under conditions of obstructed lymphatic drainage. Previous experiments by Taffel⁴ showed that the injection of organisms into the blood stream of a dog has almost no effect in the absence of lymphatic obstruction.

Reproduction of Ulcerative Colitis in Dogs

Animal	Weight, Kg.	Amount of Subcutaneous Injection, Cc.	Infecting Agent		Time After Operation to Death	Site of Disease
			Type	Amount, Cc.		
1	12	7	Bacillus coli	2.5	5 mo.	Ileum and colon
2	21	10	2 mo.	Jejunum, ileum and colon
3	19	5	B. coli	1	4 mo.	Ileum and colon
4	15	5	Staph. aureus	0.5	12 days	Ileum and jejunum
5	15	5	Str. viridans	0.5	4 days	Colon and ileum
6	12	5	Staph. aureus	0.5	2 days	Colon and ileum
7	20	5	Str. haemolyticus	0.5	8 days	Colon and ileum
8	15	5	Str. viridans	0.5	6 days	Colon and ileum
9	2.5	5	Staph. aureus	0.5	6 days	Colon and ileum
10	2.2	5	Str. viridans	0.5	5 days	Colon and ileum
11	5.1	5	Str. haemolyticus	0.5	4 days	Colon and ileum
12	15	2.5	Str. viridans	0.5	6 days	Colon and ileum
13	6.3	2.5	4 days	Colon and ileum
14	15	2.5	10 days	Colon and ileum
15	5	2.5	6 days	Colon and ileum

CONCLUSIONS

Acute and chronic enteritis, including ulceration of the mucosa of the colon, can be produced in dogs by obstructing the lymphatic drainage of the ileocecal segment of intestine. The presence of mesenteric lymphatic obstruction is sufficient to produce this ulceration of the rectal mucosa without the injection of any bacteria.

None of the organisms tested by injection appeared to have any specificity in producing ulceration of the mucosa of the colon. The more pathogenic organisms appeared to produce acute generalized enteritis rather than the chronic ulcerative form.

The mucosa of the colon has a definite tendency to ulcerate following lymphatic obstruction produced by this method, in contrast with that of the small bowel, which reacts with more acute catarrhal enteritis.

4. Taffel, M.: Experimental Production of Brain Abscesses, unpublished data.

SUBDURAL HYDROMA

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One of the complications which follow injury of the head is the accumulation of cerebrospinal fluid between the dura and the arachnoid. This is called meningitis serosa traumatica, traumatic arachnoiditis, post-traumatic subdural cyst, circumscribed hydrocephalus or subdural hydroma. Since the lesion frequently is not recognized, and the symptoms are attributed to cerebral injury, we believe a review based on our series of 19 cases is justified.

As early as 1894, Charles H. Mayo¹ reported a typical case of subdural hydroma but classified the lesion as a cerebral cyst. A boy of 12 who had sustained an injury of the head was brought to him because of severe headache, aphasia and right hemiplegia. Trephining on the left side, Mayo found in the subdural space a circumscribed collection of fluid resembling cerebrospinal fluid. The cyst was evacuated and drained; although the brain did not reexpand immediately after the operation, the late results were excellent, and complete recovery ensued.

Although Payr² described subdural hydroma, Naffziger³ was the first to give a satisfactory clinical and pathologic description of the lesion. He pointed out that the accumulation of fluid did not result from cerebral edema, as had been thought, but was the result, instead, of cerebrospinal fluid pouring into the subdural space through a tear in the arachnoid. Cerebrospinal fluid is contained within the arachnoid and normally does not enter the space between the arachnoid and the dura (fig. 1a). As a rule, none or only small quantities of serous transudate are found between these membranes at the time of craniotomy. However,

From the Section on Neurologic Surgery, the Mayo Clinic.

1. Mayo, C. H.: A Brain Cyst: The Result of Injury Causing Aphasia, Hemiplegia, etc.; Evacuation; Complete Recovery, New York M. J. 59:434 (April 7) 1894.

2. Cited by Cohen.¹²

3. Naffziger, H. C.: Subdural Fluid Accumulations Following Head Injury, J. A. M. A. 82:1751-1752 (May 31) 1924.

Penfield⁴ observed yellow coagulated masses in the subdural space in serial sections of frozen heads of normal dogs.

Since subdural hydroma develops subsequent to an injury of the head, it is reasonable to assume that a tear has occurred in the arachnoid which allows escape of the cerebrospinal fluid into the space between the arachnoid and the dura (fig. 1*b*). The arachnoidal tear usually occurs in the region of the sylvian fissure (fig. 2) or in the region of the optic

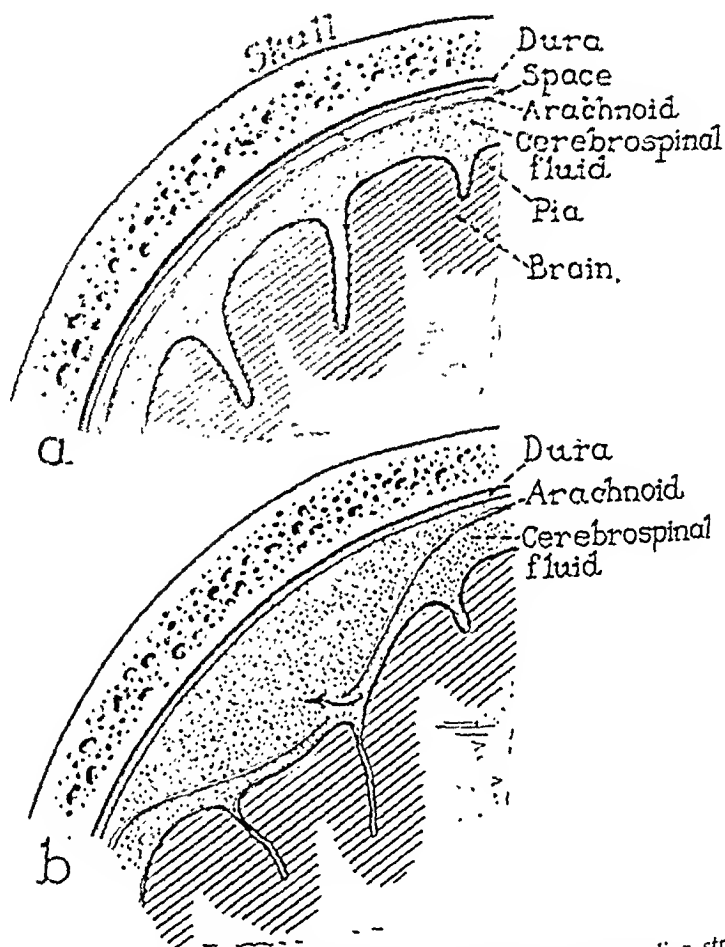


Fig. 1.—(a) Anatomic relation of subarachnoid spaces to surrounding structures; (b) hydroma, collection of cerebrospinal fluid between arachnoid and dura.

chiasm. Inasmuch as the resistance to flow of cerebrospinal fluid is less through a rent in the arachnoid than over the brain, the fluid continues to accumulate as long as the brain can be readily displaced or compressed.

4. Penfield, W. G.: The Cranial Subdural Space: A Method of Study, *Anat. Rec.* 28:173-175 (July) 1924; Chronic Meningeal (Post-Traumatic) Headache and Its Specific Treatment by Lumbar Air Insufflation: *Encephalography, Surg., Gynec. & Obst.* 45:747-759 (Dec.) 1927.

After the fluid enters the space, it becomes locked, for little or no absorption takes place. The locking process is undoubtedly due to cerebral edema which forces the brain into the arachnoid opening, thus blocking the return to the subarachnoid spaces for absorption. The collection of fluid acts as a foreign body and produces local and diffuse pressure, which interferes with cerebral circulation and gives rise to local and general neurologic symptoms. In the early phase of the lesion the fluid may contain a trace of blood, while in the chronic stage the blood has disappeared and the fluid contains xanthine and is pale yellow. In none of our cases did the fluid appear like the chocolate brown fluid of a subdural hematoma. However, it is possible for both lesions to coexist.

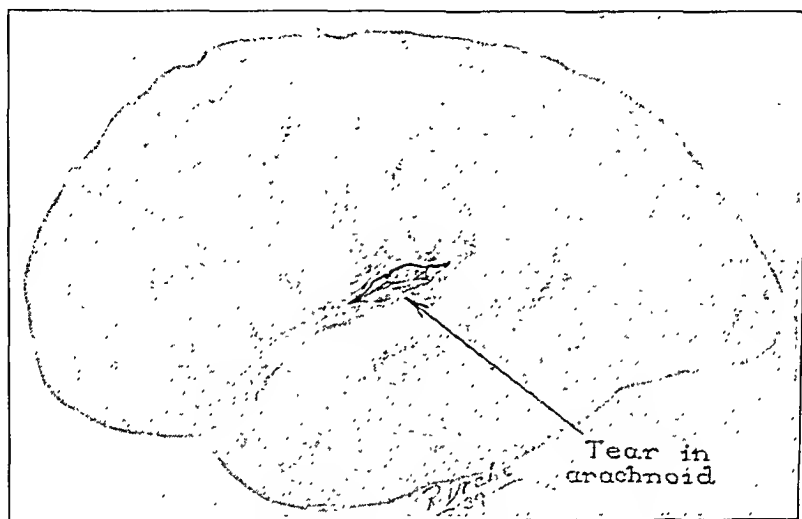


Fig. 2.—Tear in arachnoid which permitted escape of cerebrospinal fluid into subdural space.

The term “hydroma” proposed by Dandy⁵ describes the lesion better than other terms that have been used, for the lesion is not a true cyst nor has it been initiated by meningitis and arachnoiditis. Munro and Merritt⁶ were of the opinion that a subdural hydroma is only a phase of a subdural hematoma. They stated that subdural hematomas are of three types: (1) solid, (2) mixed and (3) fluid. Hematomas of the last type they

5. Dandy, W. E.: Chronic Subdural Hydroma and Serous Meningitis (Pachymeningitis Serosa: Localized External Hydrocephalus), in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1940, vol. 12, chap. 11, pp. 306-310.

6. Munro, D., and Merritt, H. H.: Surgical Pathology of Subdural Hematoma, Based on a Study of One Hundred and Five Cases, Arch. Neurol. & Psychiat. 35:64-78 (Jan.) 1936.

divided into two subgroups: (1) those in which the subdural collection of fluid consisted of a minimum of blood and a maximum of cerebrospinal fluid and (2) those in which there was only residual clear fluid because the original clots had completely dissolved during the time elapsed between the injury and the operative evacuation of the cyst. They stated that the increase of volume results from osmotic change. Gardner⁷ in experimental studies confirmed the dialyzing role of the arachnoid.

As we have stated previously, we believe that subdural hydroma and subdural hematoma may coexist and that when this happens the blood is diluted with cerebrospinal fluid, but it is our opinion that they are two separate lesions and arise from separate causes. The arachnoid undoubtedly acts as a dialyzing membrane and permits the osmotic exchange which accounts for the fluid in a chronic subdural hematoma. In our experience⁸ hydromas have been present from one day to several weeks

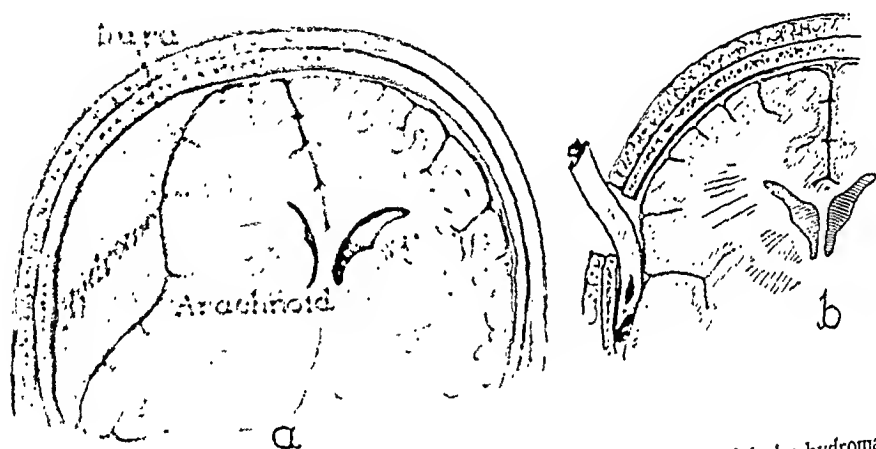


Fig. 3.—(a) Displacement of cerebrum with distortion of ventricle by hydroma; (b) drainage of hydroma with replacement of cerebral structures.

and subdural hematomas for many months before the patients present themselves for examination. Therefore, we are compelled to conclude that the hydromas were due to accumulation of cerebrospinal fluid in the subdural space and not to disintegration of blood clot, since the hydromas of a few hours' duration did not have sufficient time to develop from degeneration of blood clot. This opinion is substantiated by the case in which we demonstrated the tear in the arachnoid and the escape of fluid in the region of the sylvian fissure.

The fluid between the arachnoid and the dura may remain free or may become encapsulated with a thin membrane (fig. 3). When the hydroma

7. Gardner, W. J.: Traumatic Subdural Hematoma with Particular Reference to the Latent Interval, *Arch. Neurol. & Psychiat.* **27**:847-858 (April) 1932.

8. Adson, A. W.: Head Injuries, *South. M. J.* **32**:926-933 (Sept.) 1939.

Love, J. G.: Bilateral Chronic Subdural Hydroma, *J. Nerv. & Ment. Dis.* **85**:161-166 (Feb.) 1937.

has been of long duration, the membrane becomes thicker, although never so thick as the membrane of a subdural hematoma. The fluid has been known to coagulate when the protein content was excessively high. In the cases of Cornwall² and Abercrombie² postmortem examination revealed a voluminous semisolid mass, compressing the convexity of one hemisphere.

The subdural hydroma is more often unilateral than bilateral and invariably extends upward over the hemisphere from the sylvian fissure, but it may extend into the middle fossa. The quantity of fluid is variable. In one of Payr's cases the hydroma contained more than a pint (500 cc.) of cerebrospinal fluid, but usually only a few ounces are found. The fluid usually is under tension and may be clear, yellowish or tinged with blood in cases in which the injury has been recent. The trace of blood corresponds to the amount present in the cerebrospinal fluid. The protein content of the fluid is usually increased. In a case in our series the concentration of protein was 140 mg. per hundred cubic centimeters. Subdural hydroma is said to occur frequently, at least as frequently as acute subdural hematoma. This is not true in our groups. Owing to the larger incidence of trauma among men, hydroma is more frequent among them than among women, although it can occur in any sex or at any age.

SYMPTOMS

The symptoms and clinical findings of subdural hydroma are the same as those of subdural hematoma and are, in short, those of cerebral compression after cranial trauma. Since the subdural hydroma acts as a space-occupying lesion, focal signs such as hemiparesis, hemiplegia, aphasia, increased contralateral reflexes, unilateral mydriasis and jacksonian epileptiform attacks may develop. At other times, only symptoms of increased intracranial pressure are present, such as headache, irritability, vomiting, disorientation, grand mal convulsions, semistupor or coma, bradycardia and choked disks. However, the outstanding symptom is the headache. This is more or less severe, sharp, resistant to the usual sedatives, generalized or localized in the frontal region, behind the eyes or at the site of trauma. The headache occasionally assumes the form of hemicrania. As with subdural hematoma, mental changes varying from slight irritability or anxiety neurosis to complete dementia may develop as a result of the increased pressure or the damage of the brain with the consequent post-traumatic cortical atrophy. Focal and generalized symptoms may coexist at the same time. The symptoms, even the mental changes, may develop immediately after the injury, as in the case reported by Faure-Beaulieu and Brun,⁹ or they may appear after a free interval

9. Faure-Beaulieu and Brun: Le tréponème dans les adénopathies satellites d'arthropathies, tabétiques, abstracted, *Presse méd.* 1:42 (Feb. 17) 1932.

of longer or shorter duration, varying from hours to weeks. It is true that the free interval frequently is more apparent than real, since the patient always complains of some headache and a vague and indefinite malaise.

Roentgenograms usually do not reveal any positive sign, except possibly a previously overlooked fracture. Encephalography does not present any specific signs except the fluid level (fig. 4) or the signs described

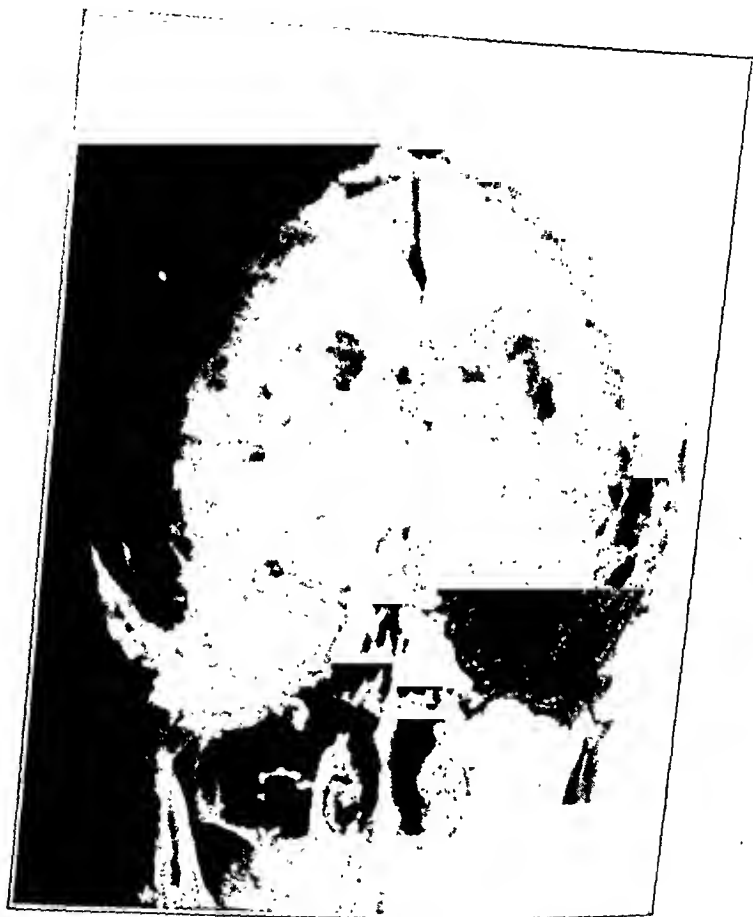


Fig. 4.—Encephalogram illustrating fluid level and spinal drainage in left parietal region.

by Dandy,⁵ Dyke^{10a} and Dyke and Davidoff^{10b} as common to the subdural hematoma.

Encephalograms reveal displacement of the ventricles and reduction in their size on the side of the lesion, that is, the signs of a space-taking

10. (a) Dyke, C. G.: Pathognomonic Encephalographic Sign of Subdural Hematoma, *Bull. Neurol. Inst. New York* 5:135-140 (Aug.) 1936. (b) Dyke, C. G., and Davidoff, L. M.: Chronic Subdural Hematoma: A Roentgenographic and Pneumoencephalographic Study, *ibid.* 7:112-147 (Sept.) 1938.

lesion, with little if any air in the subarachnoid spaces at the site of the lesion.

In the differential diagnosis, brain tumor, chronic abscess and localized meningitis must be considered and ruled out. To differentiate subdural hydroma from subdural hematoma is practically impossible, and the diagnosis often is made only at exploratory operation. As occasionally has happened in cases of subdural hematoma, the condition which has been diagnosed as brain tumor has been found at operation to be subdural hydroma.

In order to emphasize the sequence of events in the development of symptoms of patients suffering from subdural hydroma, we wish to include a detailed report of an illustrative case which Walsh and Shelden¹¹ presented at the meeting of the general staff of the Mayo Clinic.

REPORT OF A CASE

A boy 9 years of age had been thrown from his pony two days prior to admission to the Mayo Clinic. The injury took place about noon. When he was found a little later, he was unconscious and lying on his face. There was no evidence of bleeding or fractures. On being taken to his home, he regained consciousness in about an hour. However, he continued to remain drowsy and vomited, but the emesis contained no blood. He was taken to a hospital, where it was determined that his left arm and leg were partially paralyzed. On questioning, the mother stated that the paresis was less marked at the time he regained consciousness than it was at 4:30 p. m., the hour he arrived at the hospital. During the night of the first day in the hospital the boy could be aroused, although he was drowsy. The vomiting ceased, and he complained of no pain. The following day the left arm and hand appeared to be weaker than they were the day of the injury. His drowsiness had abated somewhat. Because of the symptoms he was referred to the clinic.

On admission to the clinic and hospital the patient presented left hemiparesis of the entire side, including the face. The paresis of the face was graded as 2, on a grading basis of 1 to 4, in which 1 designates the mildest and 4 the most severe condition. The paresis of the upper extremity was graded 3 and the paresis of the lower extremity was graded 1 plus. Patellar and achilles tendon reflexes were exaggerated on the left side, and the Babinski reflex was positive. Examinations of the urine and blood gave negative results. Roentgenograms of the cervical portion of the spinal column and head revealed nothing abnormal. The examination of the ocular fundi did not reveal choked disks.

Surgical Findings.—In view of the history and findings a tentative diagnosis of subdural hydroma or subdural hematoma was made, and an exploratory operation through a temporal decompression was advised and performed. The dura was uncovered in the right temporoparietal region and was found to be tense; there was no evidence of pulsations or discoloration. On perforation of the dura, blood-tinged cerebrospinal fluid spurted out. Further opening of the dura revealed a large lake of blood-tinged fluid between the dura and the arachnoid, which had

11. Walsh, M. N., and Shelden, C. H.: Acute Subdural Hydroma: Report of a Case, Proc. Staff Meet., Mayo Clin. 12:134-135 (March 3) 1937.

comprised the temporal, parietal and frontal lobes on the right side. After removal of this fluid, an illuminated retractor was introduced into the cavity in search of the rent in the arachnoid. This was found in the region of the sylvian fissure, opposite the outer margin of the wing of the sphenoid, where the arachnoid is occasionally attached to the dura (fig. 2). The opening in the arachnoid was about a centimeter in length; from this could be seen further escape of cerebrospinal fluid. Approximately 4 ounces (120 cc.) of cerebrospinal fluid was removed. As soon as the pressure had been relieved by the withdrawal of the fluid, pulsations in the cerebral artery could be seen. To remove any subsequent collection of fluid while the ventricles refilled and the brain was being replaced, a Penrose wick, a strip of gauze introduced into a Penrose drain, was inserted into the wound and left in place for four days (fig. 3b).

Subsequent Course.—During the time the drain was in place, the patient was encouraged to drink all of the fluid possible in the hope of encouraging refilling of the ventricle, replacement of the brain and obliteration of the arachnoid opening.

Convalescence was uneventful, and the wound healed by primary union. The day after the operation, the boy was much more alert than he had been prior to the operation, and the hemiparesis began to disappear. On the eighth postoperative day normal function had returned to the foot and arm, but the face and hand still showed evidence of motor weakness. On the ninth day the recovery of function in the hand and face returned overnight. He was dismissed on the fifteenth day after admission with recovery of function, except continued evidence of slight incoordination of his fingers and a slight limp on walking alone. A subsequent report from the parents indicated that complete recovery was made.

SURGICAL CONSIDERATIONS

Single or multiple trephine openings for the evacuation of encysted fluid between the dura and the arachnoid are indicated when a patient has sustained an injury of the head from which he does not promptly recover. This is especially true when the pneumoencephalographic study suggests a flattening of one or both cerebral hemispheres, with little or no air in the subarachnoid spaces in the temporoparietal region. Persistent headache after an injury is frequently the result of a subdural hematoma or a subdural hydroma and, we believe, justifies making exploratory trephine openings over the site of involvement. Occasionally, it is possible to drain this collection of fluid through a single trephine opening. However, if a large collection of fluid with marked depression of the brain is present, it is wiser to make two trephine openings over the affected hemisphere, placing one near the midline over the premotor portion of the brain and the second in the temporal region. Through and through drainage is achieved by introducing a no. 19 French catheter; this is left in place from three to five days, or until the lateral ventricles have expanded to their normal size and the space between the dura and the arachnoid has become obliterated. Although a hydroma is more often unilateral than bilateral, it usually is wise to place a trephine opening on the opposite side in a position similar to the one made over the frontal

lobe in order to make sure not to overlook a bilateral lesion. Occasionally, hydroma has a tendency to reform as in Cohen's case.¹² If this should occur, redrainage or longer continuous drainage through the temporal trephine opening will be necessary. Other procedures, such as the employment of osteoplastic flap and repeated drainage by aspiration, have been employed.

The operative results depend on the duration and the severity of the symptoms. Patients who have had symptoms of short duration without destructive cerebral changes make complete recoveries.

12. Cohen, I.: Chronic Subdural Accumulations of Cerebrospinal Fluid After Cranial Trauma: Report of a Case, *Arch. Neurol. & Psychiat.* **18**:709-723 (Nov.) 1927.

CESSATION OF RESPIRATORY EXCHANGE

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In observing the artificial state of disturbed function known as anesthesia, the anesthetist has almost constant occasion to study respiratory problems, which in other branches of medicine are encountered so infrequently as to prevent familiarity. It therefore seems to be within the anesthetist's province to offer his views on this subject. The term "cessation of respiratory exchange" is used here to refer to the complete interruption of the flow of air into and out of the lungs.

That adequate respiratory exchange is essential to life is an axiom of physiology. The layman has heard that the proof of death is to hold a mirror in front of the nose and mouth and demonstrate the absence of respiratory exchange. Even some doctors regard cessation of respiratory exchange as synonymous with death. A physician, once called to treat a person who had taken an overdose of morphine, arrived to find the patient, as he said, "already dead," although "the heart was still beating." The surest way to alarm a surgeon is to tell him that his patient is not breathing. Interrupted in the midst of a trying surgical procedure and knowing practically nothing about the preceding circumstances, the surgeon is in a dilemma, and it is not surprising that he frequently orders the administration of unavailing drugs and fails to employ the mechanical measures which might lead to successful diagnosis and treatment of the condition.

It is not the purpose of this paper to increase the alarm but rather to emphasize that cessation of respiratory exchange need not be fatal, provided it is promptly recognized, quickly investigated and judiciously treated. Failure to breathe is no more synonymous with death than is failure to eat. Either condition, if allowed to persist, will cause death from deprivation. The fact that deprivation of oxygen will cause death within seconds or minutes, while deprivation of food will cause death within days or weeks, does not alter the fundamental accuracy of this analogy. One may even point out that the urgency in each case depends on the reserve supply of certain substances in the body at the time. A debilitated patient cannot withstand starvation as long as one who is well nourished. A patient with a subnormal amount of oxygen in the blood and lungs will quickly

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succumb to cessation of respiration. On the other hand, I have seen one who had been breathing a mixture rich in oxygen live for fourteen minutes after sudden cessation of respiratory exchange. During nearly twelve minutes his original condition could almost certainly have been restored had respiratory exchange been successfully reestablished.

The conclusion is obvious. In case of cessation of respiratory exchange, supply oxygen (air) and save the life. This elementary principle is too often overlooked in the confusion of more advanced knowledge; or if the principle is recognized, its application may fail for lack of precise understanding of the mechanical factors involved.

Respiratory exchange is a mechanical function, and interference with it should be considered as a mechanical problem and treated by mechanical means. Such a viewpoint simplifies the problems of quick diagnosis and treatment required in an emergency. On a mechanical basis the instances of cessation of respiratory exchange may be divided into three classes dependent on three types of this condition.

TYPES OF CESSATION OF RESPIRATORY EXCHANGE

1. *Cessation of Respiratory Effort Without Obstruction.*—This is recognized by absence of spontaneous movement of the chest and abdomen, while efficient artificial respiration can inflate the chest, demonstrating the freedom of the air passages. It may be caused: (a) by paralysis of the muscles of respiration; (b) by excessive elimination of carbon dioxide; (c) by reflex inhibition, as from stimulation of the carotid sinus; (d) by paralysis of the respiratory center from intracranial lesions, from an overdose of sedative drugs, such as anesthetics, or from acute oxygen want. Acute oxygen want is a common sequel to other forms of cessation of respiration, or it may result from the inhalation of an atmosphere too low in oxygen. Another cause of acute oxygen want of the respiratory center always to be considered is cessation of circulation. If cardiac arrest preceded respiratory arrest, resuscitative efforts should be directed primarily toward reestablishing the circulation. This condition, however, is much less common and recovery much less likely. Indeed, there has been in the past too much emphasis on stimulation of circulation and too little emphasis on restoration of proper oxygenation. If all patients were efficiently treated on a respiratory basis, those saved would far outnumber those lost from failure to stimulate the circulation.

The immediate treatment for cessation of respiratory effort is the establishment of efficient artificial respiration. This should be accompanied by efforts to eliminate the cause. In case of an overdose of an inhalation anesthetic agent, one must provide for a free escape of exhaled gases rather than allow rebreathing of them in a closed system.

In attempting artificial respiration it is important to observe whether respiratory exchange is actually being produced. If respiratory exchange is not being successfully produced in spite of efficient efforts, the case probably belongs in the third class.

2. *Obstruction to Respiration Without Cessation of Respiratory Effort.*—This is recognized by failure to get air into or out of the lungs while active respiratory movements persist. There is a characteristic appearance to this type of futile respiratory effort with which every doctor should be familiar. The abdomen expands at the expense of the chest. It is simulated by the paradoxical "rocking boat" type of breathing caused by complete intercostal paralysis. One danger is that in the presence of respiratory efforts, the cessation of exchange may pass unnoticed until acute oxygen want becomes evident.

The causes of obstruction are so numerous that only a few examples can be mentioned here: (1) relaxation of the muscles of the jaw, as in coma or anesthesia, may permit the tongue to fall back against the posterior wall of the pharynx; (2) foreign bodies in the throat, larynx or trachea, such as chewing gum, false teeth, meat, candy, sponges, mucus, vomitus, blood or pus; (3) laryngospasm caused by local irritation or reflex stimulation; (4) tumors or edema encroaching on the respiratory passages; (5) external pressure on the neck or chest, caused perhaps by poorly fitting casts or by the weight of an intern's arm on the neck or chest of an infant.

In the treatment of obstruction, naturally the cause should be removed if possible. Pharyngeal obstruction caused by the tongue falling back may be relieved by elevating the head on a pillow and pulling the jaw forward. A semiprone position may accomplish the same result by gravity. Insertion of a good pharyngeal airway is one of the best methods of treatment. One might say without exaggeration that a good pharyngeal airway is the most valuable device in the anesthetist's armamentarium. Foreign bodies may be removed by gravity, suction, digital manipulation or instrumentation. Laryngospasm, tumors and many of the other forms of obstruction may in most cases be dealt with efficiently for the moment by the insertion of an endotracheal tube. Any obstruction at or above the larynx may be relieved by a quick tracheotomy, but other methods are preferable if they can be used successfully. In cases of obstruction it is well to remember that some air can usually be forced past the obstruction by methods of positive pressure, such as mouth to mouth breathing.

The oxygen want resulting from obstruction may become sufficiently acute to cause paralysis of the respiratory center. The case then fits into the third class.

3. *Cessation of Respiratory Effort and Obstruction to Respiration.*—This condition is recognized by absence of respiratory movements and

failure of efficient artificial respiration to produce respiratory exchange. It is caused by some combination of the causes listed for the first and second types, most commonly by acute oxygen want following obstruction or by pharyngeal relaxation resulting from the same depression which causes paralysis of the respiratory center. The first necessity is to relieve the obstruction. Then, since the patient will not resume spontaneous breathing, artificial respiration must be instituted.

REPORT OF A CASE ILLUSTRATIVE OF ALL THREE TYPES

A patient with a retropharyngeal abscess already discharging pus into the pharynx was to have the abscess drained through an external incision. As soon as anesthesia was induced, severe respiratory obstruction developed, although respiratory efforts continued (type 2). Insertion of a pharyngeal airway failed to relieve the effects of the obstruction. Signs of oxygen want were becoming rapidly apparent. An endotracheal tube was inserted with difficulty because of the swelling and distortion of the pharynx. Before this was accomplished, efforts to breathe had stopped because of acute oxygen want (type 3). The lungs were inflated several times through the endotracheal tube, and spontaneous respirations were resumed. Soon after the operation started, breathing again stopped. This time there was, of course, no obstruction (type 1). Artificial respiration by intermittent pressure on the bag had to be maintained throughout the operation, but when the surgical procedure was completed spontaneous respirations were resumed. The assumption was that cessation of respiratory exchange was due to pressure on the carotid sinus.

METHODS OF ARTIFICIAL RESPIRATION

Nearly every doctor is familiar with some methods of artificial respiration, usually the manual methods of Schafer and Sylvester. Some other methods are even more applicable in many cases. One of the quickest, most readily available and most efficient methods is that of mouth to mouth or that of mouth to nose respiration, in which the operator blows his own breath with 16 per cent oxygen into the patient. If a piece of gauze or a clean handkerchief is placed over the mouth and nose of the patient, one's esthetic senses need not be seriously offended. Most anesthetic machines with a bag, mask and oxygen tank provide a convenient means of inflating the lungs by positive pressure.

STIMULANTS

The administration of analeptics, of inhalations of carbon dioxide or of intracardiac injections of epinephrine hydrochloride is of little or no value in cases of cessation of respiratory exchange and in some cases is dangerous. In the absence of proper oxygenation the agents named will rarely stimulate the respiratory center, and they certainly can have no beneficial effect on obstruction. During respiratory arrest there is already excess carbon dioxide accumulating in the blood, and the administration of additional carbon dioxide is generally useless

and probably harmful. Intracardiac injections have no indication in relation to respiratory difficulties, and they may cause ventricular fibrillation in a heart which is still efficient.

Finally, it would be in the interests of the reputation and standing of members of the medical profession if every graduate in medicine were sufficiently capable of dealing with acute respiratory emergencies that he would not have to call on the fire department to do his work for him.

SUMMARY

Cessation of respiratory exchange need rarely prove fatal if it is promptly recognized, quickly investigated and judiciously treated.

The problem of supplying oxygen (air) to the lungs should be regarded as a mechanical one. On this basis, instances of the condition may be divided into three classes dependent on three types of difficulty: (1) cessation of respiratory effort without obstruction, in which efficient artificial respiration will inflate the lungs; (2) obstruction without cessation of respiratory effort, in which relief of the obstruction will permit spontaneous respiration; (3) cessation of respiratory effort with obstruction, in which relief of the obstruction must be followed by artificial respiration.

The physician treating the patient should not depend on the use of stimulant drugs or carbon dioxide or on the aid of the fire department.

THE BLADDER OF WOMEN AFTER OPERATION

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These studies were undertaken in an attempt to answer several puzzling questions: (1) whether or not patients having micro-organisms in the urine of the bladder before operations involving the bladder are more likely to have postoperative complications and pyelitis than are those having no organisms in the bladder; (2) whether any relationship exists between the duration of operation and of anesthesia and the incidence of postoperative catheterization; (3) whether there is any relationship between postoperative catheterization, complications involving the bladder and morbidity.

The close anatomic relationship between the bladder, the vagina, the cervix and the fundus of the uterus makes the bladder vulnerable to injury in certain types of operations. Anterior colporrhaphy involves the separation of the vaginal tissues from the anterior surface of the bladder and from the trigonal region, which is more closely attached at the cervical area. The same procedure is carried out in the Watkins interposition operation, in the Fothergill (Manchester) operation and in vaginal hysterectomy. In abdominal supravaginal and complete hysterectomy, the bladder is manipulated in separating it from the anterior surface of the uterus but to a lesser extent than in vaginal repair.

Various investigators have shown that the normal bladder of women may harbor bacteria without the development of any disease. Murray¹ of Liverpool found an incidence of 42 per cent positive cultures made from material from the bladders taken in the operating room of patients who had no urinary symptoms before operation. Not being satisfied with these results, he performed intra-abdominal puncture of the bladder in a series of 12 patients and obtained urine yielding positive cultures in 25 per cent.

The contributions of Curtis and Taussig² to the knowledge of the postoperative bladder are well known to all gynecologists. Both these observers attempted to show that residual urine was the principal causa-

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1. Williams, R. S.; Murray, H. L., and Wallace, A. J.: J. Obst. & Gynec. Brit. Emp. 22:65, 1912.

(Footnotes continued on next page)

tive factor in the production of postoperative infection of the bladder. Prior to these investigations, surgeons were rather reluctant to catheterize patients after operation, until more or less distention and discomfort had occurred.

In this field of clinical investigation, Hale-White³ should also be mentioned. He first expressed the belief that micro-organisms were not present in the urine unless there were symptoms either referable to the urinary tract or manifested by general infection. In a later paper, however, Hale-White⁴ modified his view, saying that the mere presence of colon bacilli in the urine is not necessarily productive of urinary symptoms.

It should likewise be mentioned that Williams,⁵ in 1912, made a study of patients which seemed to indicate that passage of colon bacilli in the urine was a late stage of chronic intestinal disorder and that when the intestinal condition subsided the bacilluria disappeared.

David⁶ presented a paper in 1918 showing that the injection of colon bacilli into the nonobstructed, nontraumatized bladder is not followed by cellular exudation in the submucosa or muscularis mucosae.

My investigation comprises a study of 100 patients who were subjected to major operative procedures. These procedures consisted of plastic work on the cervix or on the anterior or the posterior vaginal wall, or a combination of these, i. e., plastic operations and sections, or simply abdominal sections. Minor operations or radium implantations were not considered in this study, since the effect of the radium alone on the mucosa of the bladder may be sufficient to produce postoperative symptoms. Patients having definite urologic symptoms or those having preoperative urine with pathologic findings aside from the culture were not included in my study.

Because the term "cystitis" is vague and often loosely applied, I prefer to employ the term "postoperative pyuria," since some patients who evidence pyuria due to inflammation of the mucosa of the bladder do not have the usual train of symptoms associated with or thought to be synonymous with the condition known as cystitis; neither do I subject my patients to routine postoperative cystoscopic examination merely because pyuria of varying degree, or possibly dysuria, is present. Nevertheless, the specific diagnosis of cystitis cannot be made without inspecting

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2. (a) Curtis, A. H.: *Surg., Gynec. & Obst.* **29**:24, 1919; (b) *Management of Female Urinary Bladder After Operation and During Pregnancy: A Further Study of Residual Urine in Its Bearing on Urinary Tract Disturbances*, J. A. M. A. **80**:1126 (April 21) 1923; (c) *Surg., Gynec. & Obst.* **40**:689, 1925. (d) Taussig, F. J.: *Tr. Am. Gynec. Soc.* **40**:351, 1915.
3. Hale-White, W.: *Lancet* **2**:1203, 1912.
4. Hale-White, W.: *Lancet* **1**:1237, 1922.
5. Williams, E. M.: *Lancet* **2**:511, 1912.
6. David, V.: *Surg., Gynec. & Obst.* **26**:159, 1918.

the bladder through the cystoscope, even though there are frequency of urination, dysuria or pyuria. A cystoscopic examination should be made of those patients in whom pyuria or urologic symptoms persist.

Twenty-four patients out of the 100 included in this study were found to have a positive preoperative culture. Table 1 indicates the types of organisms recovered.

TABLE 1.—*Types of Organisms Found in Preoperative Cultures of the Urine of Twenty-Four Patients*

Bacillus coli communis.....	11
Staphylococcus albus	4
Diphtheroid bacillus	2
Streptococcus haemolyticus	1
Micrococcus ureae	2
Bacillus subtilis	1
Streptococcus nonhaemolyticus	1
Staphylococcus aureus	1
Bacillus proteus	1
	<hr/> 24

TABLE 2.—*Postoperative Course of Patients Who Had Positive Cultures Before Operation*

Patients with positive preoperative cultures.....	24
Patients with positive postoperative cultures.....	19
Patients with same kind of culture before and after operation....	10
Patients catheterized	15 (62.5%)
Patients in whom postoperative pyuria developed.....	14 (58.3%)
Patients in whom postoperative pyelitis developed.	0
Postoperative hospital days.....	18

TABLE 3.—*Postoperative Course of Patients with Positive Preoperative and Postoperative Cultures Yielding Same Type of Organism*

Patients with positive operative cultures.....	10
Patients in whom pyuria developed.....	8 (80%)
Patients catheterized	7 (70%)
Patients in whom postoperative pyelitis developed.....	0
Postoperative hospital days.....	18

The specimen for study was collected in a sterile container in the operating room after the introitus and urethral meatus had been carefully cleansed with solutions of soap, water and mercury bichloride (1 in 1,000), and it was immediately sent to the laboratory for study.

Of the 24 patients who had positive preoperative cultures, 19 had positive postoperative cultures, 10 of whom had the same organisms in the postoperative as in the preoperative cultures. Fifteen patients of the 24 (62.5 per cent) were catheterized after operation. In 14 patients

(58.3 per cent) postoperative pyuria developed; 10 of them were catheterized. Pyelitis developed in none of this group, but complications other than urologic ones developed in 3.

On further analysis of the cases of the 10 patients with the same type of preoperative and postoperative cultures, we find that 7 (70 per cent) of them were catheterized and that pyuria developed in 8 (80 per cent) of them, 5 of whom were catheterized. However, only 2 patients of this group had symptoms suggestive of cystitis, and the average number of postoperative days spent in the hospital was eighteen.

A total of 76 patients out of the series of 100 had negative cultures before operation. After operation, however, positive cultures were obtained for 39 of this group. The predominating organisms were

TABLE 4.—*Postoperative Course of Patients with Negative Preoperative Cultures*

Patients with negative preoperative cultures.....	76
Patients with positive postoperative cultures.....	39
Patients catheterized	56 (80%)
Patients in whom postoperative pyuria developed.....	28 (40%)
Patients in whom postoperative pyelitis developed.....	2 (2.0%)
Postoperative hospital days.....	19

TABLE 5.—*Postoperative Course of Patients with Negative Cultures Before and After Operation*

Patients with negative cultures before and after operation.....	36
Patients catheterized	22 (75%)
Patients in whom postoperative pyuria developed.....	5 (13.9%)
Patients in whom postoperative pyelitis developed.....	1 (2.7%)
Postoperative hospital days.....	18

B. coli communis and *Staph. albus*. Fifty-six patients (80 per cent) of the series required catheterization; postoperative pyuria developed in 28 (40 per cent), and 34 of these were catheterized. Although a higher percentage of this group with negative cultures was catheterized, pyuria developed in a relatively smaller number of them than in those who had positive preoperative cultures. Postoperative pyelitis definitely developed in 2 patients of this group. Five patients in this group complained of symptoms suggesting cystitis. The average number of postoperative hospital days was nineteen.

Thirty-six patients in the series of 100 patients had negative cultures before and after operation. Twenty-two (78 per cent) of this group of 36 were catheterized, but postoperative pyuria developed in only 5 (13.9 per cent) and pyelitis in only 1. The average number of postoperative hospital days for the group was eighteen.

Table 6 is a composite picture of tables 2, 4 and 5, relative to postoperative pyuria.

Catheterization was required much more frequently when plastic operations had been performed than when the operations consisted of abdominal sections. This should be expected, but there was not a great difference in the incidence of pyuria. In other words, although the patients who had plastic operations were catheterized much more fre-

TABLE 6.—*Postoperative Pyuria*

Patients with positive preoperative cultures in whom postoperative pyuria developed.....	14 (58.3%)
Patients with negative preoperative cultures in whom postoperative pyuria developed.....	28 (40%)
Patients with negative preoperative and negative postoperative cultures in whom postoperative pyuria developed.....	5 (13.9%)

TABLE 7.—*Incidence of Pyuria According to Type of Operation*

Type of Operation	Patients	Patients Catheterized	Postoperative Days in Hospital	Patients with Pyuria
Plastic operations.....	30	27 (90%)	10.1	13 (43.3%)
Abdominal sections.....	70	49 (70%)	21	33 (45.7%)

TABLE 8.—*Incidence of Pyuria According to Catheterization*

	Total Number	Number with Postoperative Pyuria
Patients catheterized.....	77	49 (61%)
Patients not catheterized.....	23	6 (26%)

TABLE 9.—*Relation of Length of Time Patients Were Subjected to Ether Anesthesia to Number of Catheterizations*

Time (Min.)	Patients	Patients Catheterized	Per Cent Catheterized
60 or less.....	12	10	83.3
60 to 120.....	47	38	78.3
120 to 180.....	26	19	73.3

quently than were those who had abdominal sections, pyuria did not develop in the former group as frequently as in the latter.

Seventy-seven patients of the 100 were catheterized one or more times. Pyuria developed in 49 (61 per cent). Eight patients were catheterized only once; 6, twice, and the others, more frequently. However, pyuria developed in only 6 (26 per cent) of the 23 patients who were not catheterized.

It has frequently been stated that the longer a patient is subjected to general anesthesia, the greater is the possibility that subsequent catheterization will be necessary. From my observations this appears

rather questionable. Of 12 patients on whom operations lasting sixty minutes or less were performed, 83.3 per cent were catheterized, while in 78.3 per cent of 47 patients catheterizations followed operations lasting sixty to one hundred and twenty minutes, and only 73.3 per cent of 26 patients required catheterizations following operations lasting one hundred and twenty to one hundred and eighty minutes.

These observations, however, do not take into consideration the specific type of operation performed in each case.

Fifteen of the 100 patients had spinal anesthesia, and 11 (73.3 per cent) of these were catheterized. The operative procedures in this group consisted of plastic operations, plastic operations and sections, and straight abdominal sections.

Following Curtis'⁷ suggestions, based on his experiments with animals, which tended to show that the unrelieved paralyzed bladder was a source of danger after operation, I have been liberal in my attitude toward catheterization. If a patient is unable to void eight hours after operation and the usual methods of trying to induce the patient to void are of no avail, the patient is catheterized. This procedure is then continued until the patient is herself able to empty her bladder completely.

I fully appreciate the arguments which might be urged against a study of this type because of the difficulty of obtaining urine from the bladder without contamination. It is entirely possible that the specimens from which some of my cultures were made might have been contaminated, but I feel that I created as sterile a field as possible under ordinary working conditions, for in any hospital service one has no better practical method of studying the bladder or kidney for pus and bacteria. Hence it is essential to know how much confidence one may place on the various findings mentioned.

SUMMARY

The presence of bacteria in the bladder before operation did not increase the incidence of postoperative pyelitis in this series of 100 patients. Patients with positive preoperative cultures seemed more liable to have pyuria than those with negative cultures.

Patients on whom plastic operations had been performed had to be catheterized more frequently than those on whom abdominal sections had been done.

Duration of anesthesia had some bearing on the frequency of required catheterization, but not as much as the specific type of operation, namely, plastic work.

Postoperative pyuria occurred more frequently after patients had been catheterized.

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7. Curtis (footnotes 1 a, b and c).

SPECIFIC THERAPEUTIC SHOCK—THE HUGH YOUNG REACTION

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In 1924 Young and Hill¹ described the remarkable clinical behavior of a few patients who responded favorably to the intravenous injection of mercurochrome. One of these, a man weighing about 68 Kg., had pyelonephritis and septicemia with heavy growth of colon bacilli in the blood culture. On Jan. 3, 1923, an intravenous injection of 34 cc. of a 1 per cent solution of mercurochrome was given. The temperature rose to 104 F. at midnight, but in six hours it had dropped to 97 F. The patient became rational, and on the next morning his condition was marvelously transformed, his temperature was normal, and his blood was sterile. He was discharged well on January 10.

Another man, weighing 59 Kg., with staphylococci in the blood stream, was given 10 cc. of a 1 per cent solution of mercurochrome intravenously. Following this, he had a chill, a rise of temperature above 105 F., with a fall to 102 F. in three hours and to 100 F. on the next day, and eventually recovered.

In 1925 Young² made a further report, illustrated by additional clinical charts. He said:

Among 89 cases in which I have careful notes, there was a very severe reaction in three septicemia cases which seemed hopeless. The intravenous injection of mercurochrome was followed by a fearful chill, very high temperature, and the patient went into a condition of extreme shock. One became pulseless. But all three got well, and the reporters think the drug saved them.

Later in the same article he quoted Roeder and Judd³ as follows:

We have also noted that the greater the reaction obtained the more favorable the results: temperatures rising to 106-107.5, with the urine, vomitus, and frequent fecal movement colored with the dye may appear alarming, but in our experience

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1. Young, H. H., and Hill, J. H.: The Treatment of Septicemia and Local Infections, *J. A. M. A.* **82**:669 (March 1) 1924.

2. Young, H. H.: The Treatment of Infections—General, Local and Urinary with Intravenous Injection of Mercurochrome, *Surg., Gynec. & Obst.* **40**:97 (Jan.) 1925.

3. Roeder, C. A., and Judd, W. H.: Mercurochrome Therapy, *Nebraska M. J.* **10**:41 (Feb.) 1925.

such patients have received the best results and have been harmed in no way with the exception of a salivation which has disappeared in a short time.

In my own experience the effective intravenous use of bacteriophages has frequently been associated with the production of a similar shock reaction, and this has been so often observed that I rely on the production of this reaction as an indication that adequate amounts of bacteriophage have been administered. One patient may react to a dose of 2 cc. or less, while another may require 1,000 cc. Hence administration of regularly spaced doses is advised until the chill is produced, and subsequently the therapy is continued with somewhat smaller doses at regular intervals.⁴ The reaction has been observed in numerous patients suffering from septic staphylococcemia.⁵ It is, however, also dramatic in the less common but highly dangerous invasion of the blood stream by colon bacilli.⁶ In 1 of my patients with colon bacillus sepsis the temperature rose from 104 to 108 F. and fell to 97 F. in a period of eight hours; prompt convalescence followed.

When an antibacterial serum, such as that of a horse immunized against hemolytic streptococci, has been administered intravenously in divided doses to patients with hemolytic streptococci in the blood stream, I have observed a precisely similar behavior on the part of some of the patients.⁷ I am inclined to think that this visible reaction is an indication of a turning of the balance in the fight between the bacteria, on the one hand, and the protective body fluids and phagocytic cells, on the other, probably due to an injury inflicted on the invading bacteria by the therapeutic agent, be it serum, phage or drug.

Undoubtedly this reaction has much in common with the ordinary spontaneous chill, sharp rise of temperature and sweat, so often repeated in untreated septic disease and in the earlier weeks of malaria. In its clinical character it closely resembles the shock induced by nonspecific foreign substances, such as intravenously injected triple vaccine (containing organisms of typhoid and the two paratyphoids). It differs, however, in this important respect, that it is brought about by the administration of an agent which is capable of exerting a direct specific antagonistic influence on the infecting microbe itself. The association of this reaction with intravenous therapy directed against the infecting microbe is something which belongs essentially to the more modern

4. MacNeal, W. J., and Frisbee, F. C.: Bacteriophage as a Therapeutic Agent in Staphylococcus Bacteremia, *J. A. M. A.* **99**:1150 (Oct. 1) 1932.

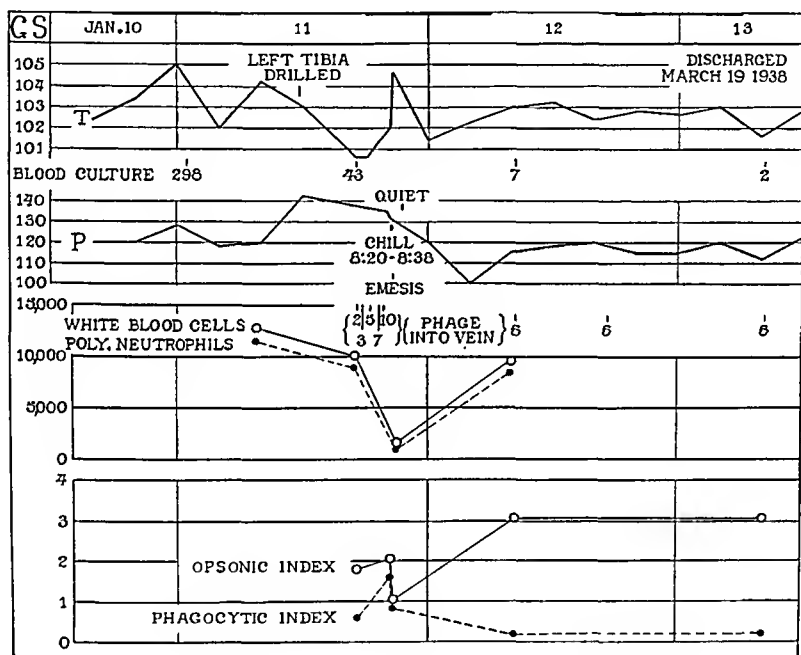
5. MacNeal, W. J.; Frisbee, F. C., and McRae, M. A.: Staphylococcemia 1931 to 1940: Five Hundred Patients, *Am. J. Clin. Path.*, to be published.

6. MacNeal, W. J.: Therapeutic Use of Bacteriophages, Particularly in Sepsis, *New York State J. Med.* **39**:451 (March 1) 1939.

7. Sheplar, A. E.; Spence, M. J., and MacNeal, W. J.: Serum Therapy for Infections with Streptococci, *Arch. Surg.* **37**:772 (Nov.) 1938.

era in therapeutics, and my associates and I⁷ have suggested that this group of phenomena, marking the successful culmination of a series of intravenous injections of an antibacterial agent, be designated as the Hugh Young reaction. A further proof of its character is furnished by the subsequent improvement in the clinical condition and the eventual recovery of the patient.

The chart illustrates the changes in the number of circulating leukocytes and in their phagocytic activity, as well as changes in the opsonic index, associated with the Hugh Young reaction in a patient



Temperature (*T*), pulse rate (*P*), blood counts, opsonic and phagocytic indexes of a patient (G. S.) with staphylococemia, Jan. 10 to 13, 1938. The patient was an 8 year old boy. He was given 27 cc. of bacteriophage in divided intravenous doses between 5:05 and 7:47 p. m. on January 11; this produced mild shock with chill, associated with a remarkable decrease in circulating leukocytes and interesting alterations in the opsonic indexes, from 8:20 to 8:38 p. m. The boy was entirely well at the time of writing.

with staphylococemia treated by intravenous injections of bacteriophage. This patient, a boy of 8 years, received stock staphylococcal phage intravenously on Jan. 11, 1938, in the following series: 2 cc. at 5:05 p. m.; 3 cc. at 5:45; 5 cc. at 6:26; 7 cc. at 7:11; 10 cc. at 7:47. A chill developed at 8:20 p. m.; it lasted eighteen minutes with a sharp rise of temperature to 104.6 F. at 8:38 and emesis of 300 cc. at 8:41.

A blood count taken at 9:03 p. m., just thirty minutes after the termination of the chill, revealed only 1,550 white cells and 992 polymorphonuclear neutrophils per cubic millimeter of blood, although the count taken at 5:03 p. m., just before the start of intravenous therapy, had shown 10,050 white cells and 8,824 polymorphonuclears and a count taken at 8:10 a. m. on the following day showed 9,600 white cells and 8,352 polymorphonuclears. The opsonic index, previously at 1.8, rose slightly during the intravenous therapy to 2.1 at 8:24 p. m. (just after the chill started at 8:20) and fell abruptly during the chill to 1.1 at 8:45 p. m., and rose to a high level, 3.1, on subsequent days. The comparative phagocytic activity of the patient's leukocytes (phagocytic index), which before treatment was 0.6 at 5:04 p. m., increased during the intravenous therapy to reach 1.6 at the beginning of the chill (8:24 p. m.) and fell abruptly to 0.8 at 8:45 p. m., after the chill had ceased. Subsequently the phagocytic index remained low until the bacteria were no longer present in the circulating blood (January 24). Evidently, in the presence of opsonized bacteria the leukocytes capable of phagocytic activity are to a considerable extent used up and lost from the blood.

These observations on human patients are in accord with studies of bacteriophage behavior in vitro and in experimental animals,⁸ and they permit one to visualize the mechanism of the Hugh Young reaction. Evidently the therapeutic agent alters the infecting bacteria so as to render them more susceptible to phagocytosis (opsonic effect). The circulating leukocytes then take up these invading microbes, and at the same time the fixed phagocytic cells in the liver, spleen, lymph nodes and bone marrow participate in this more active phagocytosis. The phagocytic wandering cells, injured in this activity, are in turn phagocytosed by the reticuloendothelial cells of the internal organs, and hence a relative excess of young granulocytes of feeble phagocytic power remains in the circulating blood. The augmented destruction and digestion of bacteria and of host cells incident to this combat release various toxic substances to induce the chill and febrile reaction.

It is, however, quite probable that other, nonspecific (pyrogenic) substances may sometimes play a part and confuse the picture. Thus, the patient may be sensitive to the animal serum used, or the medium employed to dissolve the drug or that in which the bacteriophage is administered may itself contain such pyrogenic substances. Careful consideration should be given to these possibilities in each instance.

8. MacNeal, W. J.; Frisbee, F. C., and Slavkin, A. E.: Mechanism of Bacteriophage Action in Staphylococcus Bacteremia, *Proc. Soc. Exper. Biol. & Med.* **30**:12 (Oct.) 1932. MacNeal, W. J.; McRae, M. A., and Colmers, R. A.: Further Observations on Bacteriophage Action in the Presence of Blood, *J. Infect. Dis.* **63**:25 (July-Aug.) 1938.

ACUTE INTUSSUSCEPTION

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Acute intussusception is a clinical and surgical emergency which can be completely and permanently cured by immediate and competent surgical intervention. On the other hand, tragedy often results if indecision and procrastination have occurred before the institution of treatment. Chronic intussusception more often than not is of secondary importance, and the primary pathologic process, usually a tumor, demands planned surgical attention.

One hundred and seventeen cases of intussusception in which operation was performed at the Mayo Clinic were reviewed. In 55 of these cases the condition was classified as acute intussusception. In this paper only data concerning the cases of acute intussusception are included. Thirty-eight of the patients were boys, and 17 were girls; this represents an incidence of 2.2:1.

Acute intussusception is primarily a disease of childhood, in contrast to the chronic process which nearly always manifests itself in adults. The youngest of our patients with acute intussusception was 24 days old; the oldest was 13 years of age. Thirty-six, or 65 per cent of the patients, were less than 1 year old, and 44, or 80 per cent, were less than 2 years of age.

In none of these cases was there any recurrence after surgical reduction. In 9 there had been recurrent mild attacks of abdominal cramps which finally ended in the acute process; in the other 46 cases, the acute episode marked the primary clinical attack. The recurrent attacks extended over periods of a few days to fourteen weeks before the onset of the acute symptoms that finally led to diagnosis and subsequent surgical treatment.

In all the cases in this series, as is usual in acute intussusception, the process was ileocolic; the intussusceptum or head of the process, starts in the terminal part of the ileum, moves into the cecum and thence, if the process continues, progresses up the ascending colon, on through the rest of the large bowel and may even present at the anal outlet.

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CAUSE

According to the reports of others and our own judgment, it is unusual to find a definite pathologic basis for the event, with the exception of an occasional Meckel's diverticulum, which seemed to be the causative factor in 2 of our cases. The other 53 cases belong to that group in which there is no definite causative process.

Several explanations have been offered concerning the pathogenesis of this condition. The most tenable seems to be that fostered by Perrin and Lindsay.¹ The ileocecal valve of the infant projects $\frac{3}{8}$ inch (1 cm.) into the cecum and the terminal part of the ileum receives a rich supply of lymph. Because of digestive disturbances, which are most likely to occur after the fifth month of life, when changes in diet are made, the lymphatic structures become swollen, and the terminal part of the ileum projecting into the cecum acts as an irritant. The increasing peristalsis results in intussusception. It is possible that the severe intestinal colic of children from which recovery is spontaneous may be an early stage of the process with spontaneous reduction and cessation. Another explanation is that the condition is purely neurogenic. Uncoordinated nervous impulses which contract the intestines here or there and stimulate peristalsis or antiperistalsis above or below the contracted part could easily lead to telescoping of the segment. Uncoordinated nervous impulses as a causative factor would also explain the rare retrograde or even the multiple intussusception. Either of these theories would certainly depend on the mobile terminal part of the ileum, cecum and colon, which is normally present in the infant.

SYMPTOMS AND DIAGNOSIS

The symptoms and findings in acute intussusception usually follow a rather stereotyped pattern. The diagnosis is not often an involved problem, but early diagnosis is of the utmost importance. In 11 of the 13 cases of this series in which death occurred, the patients had had definite symptoms for at least twenty-four hours before operation, while for many more than half the patients who survived diagnosis was made and operation was performed within twenty-four hours after the onset of acute symptoms.

The most constant and pathognomonic symptom is the characteristic intermittent colicky abdominal pain. In every one of the cases it marked the onset of the train of symptoms and findings that led to the ultimate diagnosis. In a typical instance, a healthy child suddenly will double up and cry out from severe pain, which after a few moments usually leaves as suddenly as it came. As the disease progresses, the attacks of pain

1. Perrin, W. S., and Lindsay, E. C.: Intussusception: Monograph Based on Four Hundred Cases, *Brit. J. Surg.* 9: 46 (July) 1921.

continue at varied intervals. Vomiting is generally an early and prominent symptom of the disease. Shortly after the onset, the child may have a bowel movement which consists mostly of mucus and the feces that happen to be in the lower part of the bowel at that time. This usually is followed by spells of tenesmus and passage of mucus and blood. Bloody discharge from the rectum usually occurs at one time or another during the progress of the process. It may not be noted until it is seen on the examining finger of the physician, or it may have been seen in the returns of an enema administered by a frustrated parent trying to alleviate the pains of the suffering infant. In 43 of our cases either there was a history of blood or blood-tinged material being passed from the rectum, or blood was noted at the time of examination.

The patient who has acute intussusception is usually less than 2 years of age and of normal healthy development. Between colicky pains, the child generally lies quiet and for the most part is easy to examine. During the periodic attacks, however, the legs will be drawn up with pain. Careful abdominal and rectal examination usually will reveal a sausage-shaped mass in the right side of the abdomen. Failure to elicit a mass, however, does not rule out the diagnosis. In 15 of our cases a palpable mass was not noted on physical examination. After the child is anesthetized, it is not unusual to feel a mass which escaped detection in the preliminary examination.

The foregoing relates the typical chain of events. Intermittent colicky pains alone, without the other signs and symptoms of intussusception, should be looked on with suspicion, and progression of events into the typical picture of this pathologic process should demand prompt surgical intervention.

TREATMENT

It is our opinion, as well as that of the majority of those who come in contact with this disease, that prompt surgical intervention is the only rational treatment of this condition. There are still a few proponents of medical reduction through the use of intracolonic pressure by means of introduced barium sulfate, water, gas or other mediums. At best, those methods have a definite proportion of recurrences that demand later surgical treatment and, furthermore, it is impossible to know that the process has been entirely reduced. Delayed surgical intervention, owing to the failure of medical measures, will serve only to increase greatly the mortality.

Drop ether anesthesia is well accepted as the method of choice for infants. A right paramedian incision is made in the abdomen. In most of these cases the pathologic condition can be righted by simple manual reduction, that is, gentle milking from below upward with only the slightest traction on the proximal loop. In 44, or 80 per cent, of the cases

in this series reduction was accomplished by this method. If the process cannot be reduced completely because of edema of the tissues, cutting of the constricting neck of the intussusception with scissors and subsequent repair of the wall of the bowel, as described by Brown,² may well be considered. Gangrenous bowel, irreducible masses and marked obstruction demand separate attention, and we shall refer to these later.

Many different methods are described to prevent recurrences of the condition. Although recurrence is unusual after surgical reduction, the possibility must be kept in mind, and in each instance the decision must be made from the findings at operation whether some method of preventing recurrence should be adopted. In 16 of the cases in this series, simple reduction and nothing more was done. In 9 cases, after reduction the appendix with the ligated mesoappendix was brought out through a stab wound to serve as an anchoring point for the cecum. With this procedure, a catheter usually is introduced through the appendical stoma to serve as a decompression valve. The appendix usually sloughs off in eight to ten days, or it may be removed with the cautery when convenient. The resultant fistula closes spontaneously as a rule, or, if a little drainage persists, it may be necessary to destroy the lining of the mucous membrane with the cautery. This procedure will insure prompt closure. In 8 of our cases the terminal part of the ileum was sutured to the cecum or ascending colon after reduction to prevent recurrence. In 5 cases the mesentery was shortened and in 5 the cecum was stitched to the parietal peritoneum for the same purpose.

When gangrenous or necrotic bowel is encountered, either exteriorization or resection with primary anastomosis is indicated. The former seems to be the procedure of choice at most times. Primary anastomosis because of its attendant high mortality rate should be reserved for the rare occasion. The latter procedure was performed in 5 cases in this series with two deaths.

A fixed irreducible mass is probably best treated by a short-circuiting anastomosis. This was done successfully in 3 of our cases with no hospital mortality. Ileostomy alone or combined with one of the other procedures might be demanded when marked obstruction and distention are present. Two of our patients who underwent primary ileostomy subsequently passed sections of necrotic bowel through the rectum. The case of 1 of these patients was reported in detail elsewhere.³ In both instances short-circuiting procedures were done later because of incomplete obstruction.

2. Brown, H. P., Jr.: *Acute Intussusception in Children: Observations on Thirty-One Cases Admitted to the Children's Hospital in Philadelphia*, *Ann. Surg.* **81**:637-645 (March) 1925.

3. Mayo, C. W.: *Acute Intussusception*, *Nebraska M. J.* **18**:121-125 (April) 1933.

HOSPITAL MORTALITY AND SUGGESTIONS FOR DECREASING IT

In this series of cases of acute intussusception, the hospital mortality rate was 23.6 per cent. Surgical shock, superimposed on the toxemia and on the already depleted system of the infant, is the chief factor in the hospital mortality. In 10 of the 13 fatal cases in this series death occurred within a few hours after operation and could be attributed only to those factors. Peritonitis, ileus and pneumonia were contributing factors in the other 3 cases. Of course, early surgical intervention assumes the utmost importance if the child is to be brought to operation in better condition. We feel, however, that more must be done to combat the toxic reaction and refurbish the depleted system before operation is undertaken. It is with that in mind that lately we have been preceding the surgical intervention with a small transfusion of blood, and we have been giving fluids and electrolytes intravenously in the course of the operation to bring the concentrations into the normal range. This transfusion can be taken care of while the operating room is being set up, and if a blood bank and a separate transfusion team are available, it can be completed without any appreciable delay in the operation. Our custom is to use group IV blood (Moss classification) without taking time to type or cross match the blood. There have been no fatal outcomes in the few cases in which this additional treatment has been administered, and we hope that further use of it will materially reduce our mortality rate. Oxygen, too, must be kept in mind as an additional agent of value in our armamentarium.

SUMMARY AND CONCLUSIONS

Fifty-five consecutive cases of acute intussusception which came to operation at the Mayo Clinic are reviewed. The disease is primarily one of infancy and early childhood. The condition attacks otherwise healthy infants, and its ultimate outcome depends a great deal on an early diagnosis followed by prompt surgical intervention. Surgical shock, superimposed on the toxic reaction and the depleted system, is the immediate cause of death in the great majority of fatal cases. Lessening of the mortality rate for this condition seems to depend on earlier diagnosis and treatment supplemented by supportive and replacement therapy before and during the operation.

GIANT INTRACANALICULAR FIBROADENOMA OF THE BREAST

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A varied and confusing picture is presented by the breast tumor first described by Chelius¹ in 1828 as a "cystic hydatid." Several specimens were described in more detail by Johannes Müller² in 1838 under the name of "cystosarcoma phyllodes." The confusion regarding the character and behavior of this interesting tumor is well brought out in the list of names employed in describing the 121 examples which have been reported to date. These various names are as follows:

- Cystic hydatid—Chelius¹ 1828
- Cellular hydatid—Cooper³ 1829
- Cystosarcoma—Fischer⁴ 1835
- Cystosarcoma phyllodes—Brunn 1838 (published by Müller²)
- Hydatid tumor of the breast—Warren⁵ 1839
- Serocystic tumor—Brodie⁶ 1846
- Cystic sarcoma—Erichsen⁷ 1852
- Telangiectatic cystosarcoma—Amado⁸ 1872
- Proliferous cystosarcoma—Gross⁹ 1874

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1. Chelius: *Telangiectasie*, Heidelb. klin. Ann. 4:449, 1828.
2. Müller, J.: *Ueber den feinern Bau und die Formen der krankhaften Geschwülste*, Berlin, G. Reimer, 1838.
3. Cooper, A. P.: *Illustrations of Diseases of the Breast*, London, Longman, Rees & Co., 1829, p. 32.
4. Fischer: *Cystosarkom der rechten Mamma; Extirpation; Heilung*, Ztschr. f. Wundärzte u. Geburtsh. 33:223, 1882.
5. Warren, J. C.: *Surgical Observations on Tumours*, London, J. Churchill, 1839.
6. Brodie, B. C.: *Lectures on Various Subjects in Pathology and Surgery*, London, Longman [and others], 1846, p. 148.
7. Erichsen: *Recurrence of Cystic Sarcoma of Breast*, *Lancet* 1:120, 1852.
8. Amado, S.: *Un caso de kisto-sarcoma telangiectasico e papillar da glândula mamaria do homem*, J. Soc. d. sc. med. de Lisboa 36:56, 1872.
9. Gross, S. W.: *Proliferous Cysto-Sarcoma of the Breast*, Tr. Path. Soc. Philadelphia 4:216, 1874.

- Intracanalicular papillary fibromyxoma—Bigelow¹⁰ 1876
 Intracanalicular sarcoma—Iverson¹¹ 1877
 Intracanalicular myxofibroma—Watson¹² 1878
 Intracanalicular papillary fibromyxoma—Watson¹² 1878
 Sarcoma with lacunar cysts—Raingeard¹³ 1882
 Intracanalicular myxoma—Jüngst¹⁴ 1884
 Proliferating cystic tumor—Leser¹⁵ 1888
 Cystosarcoma—Schmidt¹⁶ 1889
 Cystosarcoma mammae proliferum—Noetzel¹⁷ 1892
 Papilloma intracanaliculare—Kurstainer¹⁸ 1894
 Intracanalicular fibroma—Pearce¹⁹ 1895
 Intracystic mammary sarcoma—Snow²⁰ 1899
 Cystofibrosarcoma—Grohé²¹ 1900
 Pearly cystosarcoma phyllodes—Beneke²² 1902
 Adenoma pseudosarcomatodes—Beneke²² 1902
 Fibroadenoma intracanaliculare papillare—Schmuckert²³ 1904
 Adenomyxofibroma intracanaliculare papillare—Gorham²⁴ 1911
 Fibrolipoadenoma intracanaliculare sarcomatodes xanthomatodes mammae—Binckert²⁵ 1924

10. Bigelow: Tumor of the Breast: Intra-Canalicular Papillary Fibromyxoma, Boston M. & S. J. **94**:581, 1876.

11. Iverson, A.: Cysto-sarcoma mammae, amputatio mammae, Hospitalstid. **4**: 331, 1877.

12. Watson, A.: Ueber das Fibro-Adenom der Mamma, Inaug. Dissert., Göttingen, W. F. Kaestner, 1878.

13. Raingeard: Tumeur du sein, Bull. Soc. anat. de Nantes **6**:39, 1882.

14. Jüngst, C.: Ein intracanaliculäris Myxom der Mamma mit hyaliner Degeneration, Virchows Arch. f. path. Anat. **95**:195, 1884.

15. Leser, E.: Beiträge zur pathologischen Anatomie der Geschwülste der Brustdrüse, Beitr. z. path. Anat. u. z. allg. Path. **2**:379, 1888.

16. Schmidt, G. B.: Die Geschwülste der Brustdrüse, Beitr. z. klin. Chir. **4**:78, 1889.

17. Noetzel, W.: Ein Beitrag zur Kenntnis der Fibroadenome der weiblichen Brustdrüse, Inaug. Dissert., Berlin, G. Schade, 1892.

18. Kurstainer, W.: Adenoma der Milchdrüse mit cylindrischem und geschichtetem zum Theil verhorntem Epithel, Virchows Arch. f. path. Anat. **95**:195, 1884.

19. Pearce, F. L.: Further Report on Intercanalicular Fibroma of Right Mammary Gland, Tr. Path. Soc. Philadelphia **17**:157, 1895.

20. Snow, H.: Large Intra-Cystic Mammary Sarcoma Removed by Operation, Brit. Gynaec. J. **15**:157, 1899.

21. Grohé, B.: Ueber Cystofibrosarkome der Mamma mit epidermoidaler Metaplasie, Deutsche Ztschr. f. Chir. **55**:67, 1900.

22. Beneke: Ueber die Adenofibrome der Mamma, Verhandl. d. deutsch. path. Gesellsch. **4**:205, 1902.

23. Schmuckert, K.: Adenofibroma der Mamma übergehend in Adenosarcoma, Munich, C. Wolf & Son, 1904, p. 24.

24. Gorham, W.: Adeno-Myxofibroma papillare intracanaliculare mammae mit Sarkom und Epidermiseysten, Strassb. med. Ztg. **8**:121, 1911.

25. Binckert, M.: Fibrolipoadenoma intracanaliculare sarcomatodes xanthomatodes mammae, Frankfurt. Ztschr. f. Path. **30**:498, 1924.

Giant intracanalicular myxoma—Lee and Pack²⁶ 1931

Giant intracanalicular fibroadenomyxoma—Smith²⁷ 1935

Intracanalicular fibroadenoma—Mackenzie²⁸ 1935

In 1931 Lee and Pack²⁶ published an excellent and exhaustive review of the literature on this tumor. They collected 105 cases and added 4 cases from their own clinical material. They suggested that the term "giant intracanalicular myxoma" should be adopted.

Since Lee and Pack's review, at least 12 similar cases have been reported, although still with the same confusion of nomenclature. One of 7 cases reported as instances of sarcoma of the breast by Schreiner and Thibaudeau²⁹ in 1932 almost certainly was a case of the tumor in question. The patient was a woman of 78 years. For eight years she had noted gradual growth of a small tumor of the breast until it reached tremendous size. This tumor, removed by simple excision, measured 63 by 30 cm. and weighed 16 pounds (7.3 Kg.). The patient was well and showed no evidence of recurrence five months later. The description of the tumor was as follows:

On gross section of the breast, a dense white fibrous growth, in places attached to the skin surface, was disclosed. This tumor showed a glistening gelatinous surface and in places the substance is translucent. Some haemorrhagic areas were found scattered throughout the tumor and a few cysts filled with thin, stringy, gelatinous fluid. Microscopical sections showed a connective-tissue tumor made up of fibrous connective-tissue cells of embryonic type with, in many places, large areas where myxomatous changes had occurred. Some areas of necrosis are found scattered throughout the section. Marked proliferation of the smaller blood-vessels was a rather general occurrence throughout the tumor with some areas of haemorrhagic deposit. In some fields the tumor has become more cellular with the presence of many spindle-shaped cells. Diagnosis.—Myxofibrosarcoma.

The description and the illustrations fit nicely into the category of cystosarcoma phyllodes, and one is led to wonder if this may not be such a tumor.

In 1935 Smith²⁷ reported 2 cases. One patient was a woman of 44 years who had noted a small lump in her breast for ten years. No change of size had been noted until six months prior to her operation, when there was sudden and rapid enlargement of the mass to the "size of a large orange." The tumor showed typical gross and histologic characteristics.

26. Lee, B. J., and Pack, G. T.: Giant Intracanalicular Fibroadenomyxoma of Breast: The So-Called Cystosarcoma Phyllodes Mammæ of Johannes Müller. *Am. J. Cancer* 15:2583, 1931; *Ann. Surg.* 93:250, 1931.

27. Smith, I. H.: Giant Intracanalicular Fibroadenomyxoma of the Breast. *Am. J. Surg.* 30:545, 1935.

28. Mackenzie, K.: Huge Fibro-Adenoma of the Breast, *Brit. J. Surg.* 23:234, 1935.

29. Schreiner, B. V., and Thibaudeau, A. A.: Sarcoma of the Breast, *Ann. Surg.* 95:433, 1932.

The second patient was a woman of 30 years who had noticed a lump for three years. During the twelve months prior to admission the tumor had grown rapidly to a mass measuring 8 cm. in diameter. This mass also was pathologically typical for the group of tumors here discussed.

Mackenzie²⁸ reported in 1935 a patient of 34 years who had noticed a rapid increase of size in a small breast nodule, which when removed was found to weigh 35 pounds (15.9 Kg.). The tumor was called an intracanalicular fibroadenoma. There was no recurrence after simple mastectomy.

In a discussion of sarcoma of the female breast in 1935, Rose³⁰ reported 2 cases of "cystosarcoma" of the breast. One of the tumors was in a woman of 33 years. She had noted a small lump in the breast for two years, but in the month prior to her operation the mass had suddenly grown rapidly to tremendous size. The other patient, a woman of 28 years, had noted a small sessile mass in the breast for one year. In four months it had reached massive proportions and had ulcerated. Both were cured by excision. The microscopic features of the tumors were typical.

In 1936 Markowitz and Howell³¹ reported a tumor of this sort in a 14 year old girl. In two months the breast had enlarged to twice normal size and contained a mass measuring 11 by 14 cm. Simple excision effected a cure.

In 1938 Funck-Brentano and associates³² reported 5 cases. The average age of the patients was 38.7 years, and all gave a history of a small sessile mass in the breast quiescent for variable periods which then suddenly grew to alarming proportions in a period of about a year. One gave a history of gradual growth for five years, another a history of rapid growth for fifteen days, while the rest reported rapid growth over a period of eight or nine months. These tumors had all of the gross and microscopic characteristics of the "giant intracanalicular myxoma."

Under the name "giant intracanalicular fibroadenomyxoma" a case of the tumor in question was reported by Desai³³ in 1939. The patient, a single woman of 44 years, had been aware of a small hard tumor in her breast for eighteen years. She injured the breast in an accident in 1935, and after this there began a slow enlargement of the breast. The progres-

30. Rose: Die Sarkome der weiblichen und die Geschwülste der männlichen Brustdrüsen nach dem Material der chirurgischen Klinik zu Leipzig, Deutsche Ztschr. f. Chir. **246**:151, 1935.

31. Markowitz, B., and Howell, H. L.: Rapid Growth of a Large Breast Fibroma in a Young Girl, J. A. M. A. **107**:1043 (Sept. 26) 1936.

32. Funck-Brentano, P.; Bertrand, I., and Poilleux, F.: Les tumeurs phyllodes du sein. (Cysto-sarcoma phyllodes de Johann Müller), J. de chir. **51**:506, 1938.

33. Desai, P.: Le fibro-ado-éno-myxome intracanaliculaire géant du sein, type phyllode de Johann Müller, Ann. Soc. méd.-chir. de Liège, 1938, pp. 239-248.

sion of the lesion continued until it ulcerated and herniated in 1938. The breast was removed at that time; the tumor mass weighed 4.9 Kg. The gross and microscopic appearance of the tumor was typical, and the patient was free from any recurrence six months later.

A review of the main features described brings out certain developmental and morphologic peculiarities of this tumor. The clinical history of the condition may simulate that of sarcoma of the breast in that there is rapid growth of a mass in the breast to a large size. However, in almost every case there will be a history of a preexisting mass in the breast. This remains quiescent for a number of years, then rapidly enlarges and grows to alarming proportions. Some of these tumors weigh as much as 20 Kg., and the average weight of the reported ones is 7.6 Kg.

Enlargement may progress to such proportions that rupture of the skin occurs with herniation of cauliflower-like masses through the opening. Pain is not a prominent symptom, and the only complaints are apt to be the size of the breast or the disability resulting therefrom. Sarcomatous degeneration with metastasis has been known to occur. However, simple amputation of the breast mass is ordinarily successful in effecting a cure, although there may be local recurrence.

The tumor warrants pathologic study because of its resemblance to and confusion with sarcoma. Externally the breast is bosselated with variable regions of fluctuation and resistance. When the breast is cut, the tumor is found to consist of huge, well encapsulated intracystic polypoid masses with narrow tortuous clefts, which contain thin fluid ranging in color from yellow to brown. As enlargement progresses, the polypoid masses tend to become flattened and may completely fill the cystic spaces, so that the tumor appears solid. The cut surfaces show great variation, having degenerating zones alternating with areas of solid tissue. Scattered throughout and constituting the majority of the solid parts of the tumor is a soft semitransparent tissue. There is a strong limiting capsule about the tumor, and no invasion of the surrounding tissues occurs.

Histologically the tumor shows variation closely paralleling the gross appearance. The close structural resemblance of the entire tumor to intracanalicular fibroadenoma is striking. Buds of connective tissue project for varying distances into spaces which are slitlike in character, and none of these numerous slitlike spaces is without epithelial lining. Polymorphism of the stroma is remarkable. Sclerotic plaques composed of cellular areas with dense masses of collagen are scattered among myxoma-like regions or areas of edematous infiltration. No bone or cartilage is present. The amount of necrosis and hemorrhage varies in direct proportion to the size of the tumor.

REPORT OF A CASE .

Mrs. G. K., the patient, was 37 years old, white, nulliparous and married. The family and personal history were irrelevant, save for the complaint of disturbances associated with her menses. Menstruation began at 13 years with periods at intervals of thirty days, lasting five to six days. However, she always suffered severe dysmenorrhea with nausea and vomiting on the second day, and for three or four months had noted some bleeding between periods. Her last menstrual period was two weeks before admission on July 10, 1940.

At this time she had known of a mass in her left breast since July 1939. This had appeared in the inferolateral quadrant of the breast, was hard, circumscribed and covered with tense skin. During the summer of 1939 the mass gradually enlarged, and the entire breast then became swollen and tender. Tenderness was most marked just preceding the menstrual period. No discharge from the nipple

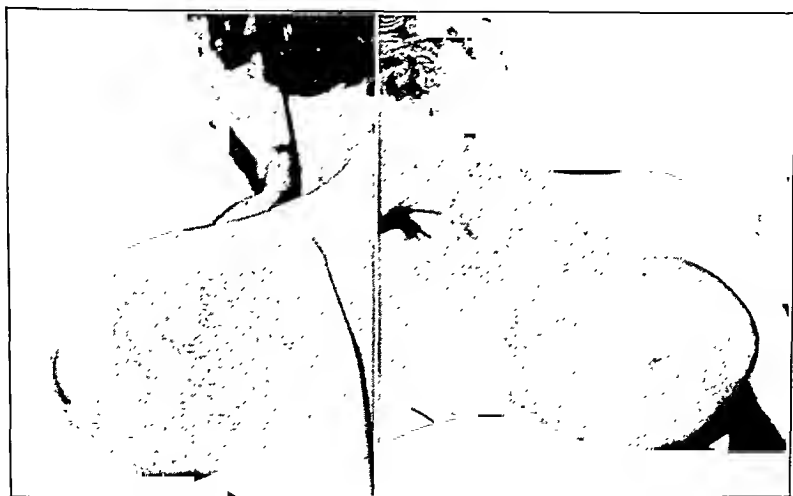


Fig. 1.—Two views showing the appearance of the breast on admission.

and no dimpling of the skin were noted. In the winter of 1939-1940 the patient noted that the breast was rapidly enlarging, so that it became twice the size of the right breast. She also noted two reddened areas in the skin about 3 to 4 cm. in diameter. These rapidly became blue, and the entire breast became hot and more tender, while the skin over the breast became tightly stretched. About a month later the breast suddenly softened and became smaller. During the spring of 1940 the mass changed little and bothered the patient only slightly. Two days prior to entry the patient had a chill and became ill with "flu." Within thirty-six hours the breast had grown to twice its size of the previous several months. It became tense, reddened and then turned dark grayish blue. She had suffered no loss of weight, but on the contrary had gained 8 pounds (3.6 Kg.) in the preceding seven months.

On admission the patient appeared acutely ill and was febrile (temperature, 101 F.); her pharynx and larynx were congested. The left breast, swollen to four times the size of the right, was tense and tender. The lateral surface was reddened and hot, and the inflammation extended around to the posterior axillary

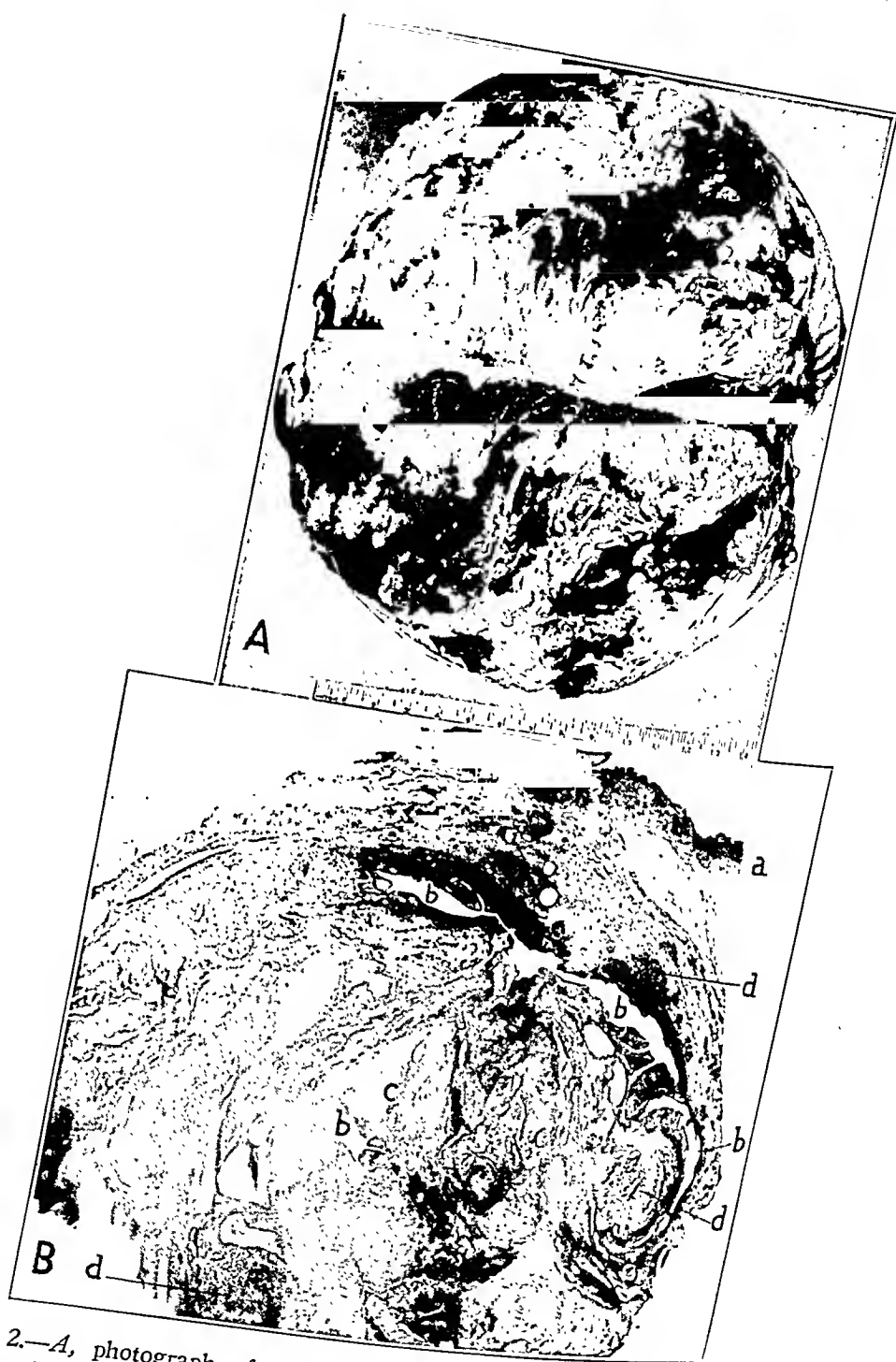


Fig. 2.—*A*, photograph of the gross specimen divided in half. Note the irregular cleftlike spaces which contained thin yellowish fluid. *B*, low power magnification of a microscopic section taken through most of the tumor mass. Note (*a*) skin overlying the tumor, (*b*) irregularly sized and shaped spaces, (*c*) partially necrotic and markedly edematous connective tissue and (*d*) widely scattered nests of gland elements.

line. The entire breast appeared fluctuant, and there were several intensely red areas in which the skin was shiny, thin and stretched taut. Just below the normal areola was a slightly elevated bluish area which transluminated and felt fluctuant.

With the diagnosis of acute abscess of the breast, a 4 cm. radial incision was made in the upper outer quadrant of the breast in the region of maximum fluctuation. A large cyst containing about 100 cc. of a yellowish brown turbid serous material was broken into. The entire breast seemed to be composed of a grayish friable tissue honeycombed with cystic areas containing a turbid serous material.

Microscopic examination of fragments of the tissue led to a diagnosis of cytosarcoma phyllodes. Cultures of the fluid from the cystic cavity were sterile.

Seventeen days later, after the subsidence of the acute infection of the upper respiratory tract, a simple mastectomy was performed. A few of the superficial fibers of the pectoralis major muscle were removed with the breast. The gross specimen weighed 2,650 Gm. and measured 9 by 15 by 20 cm. A central round firm mass with small fluctuant areas occupied the major portion of the breast (except for about 1 to 2 cm. around the periphery). The ellipse of skin excised with the mass included the areola and the nipple. The skin was of normal texture and was not fixed to the tumor; the nipple was not inverted. Also, the tumor was not adherent to the resected portion of the pectoral muscle.

A cut surface of the mass showed many cystic spaces from a few millimeters in diameter to a large cyst, 3 cm. in diameter, which communicated with the surgical drainage wound. The cysts were filled with a slightly turbid brownish yellow fluid. Much of the stroma of the tumor appeared translucent, and from these areas fluid escaped when a fresh cut was made. The main tumor mass was well demarcated peripherally and was surrounded by a firm fibrous capsule which could be separated with ease from the mass. The outer parts of the tumor appeared yellowish white and seemed to be made up of strands radiating out from the central portion.

In spite of slight secondary infection of the operative wound, healing was rapid and entirely satisfactory. Eight months subsequent to her operation the patient was quite well, and there was no sign of any recurrence.

In sections from different portions of the tumor mass the gland spaces varied from closely grouped small acini to large cystic spaces. There was a corresponding variability of epithelial linings. In some acini the epithelium was a single-layered cuboidal epithelium, while in still other areas the cells were cuboid but piled up in several layers. A great deal of desquamation of epithelial cells into the glandular lumens was evident. Many of the larger spaces were lined by a single layer of flattened cells. Immediately beneath the epithelium of the gland spaces was a single layer of large clear cells with rather large round nuclei. Much of the stroma of the breast was made up of dense sheets of hyperchromatic spindle-shaped cells. These cells were arranged in streams in a fairly orderly fashion between the glandular structures. Many club-shaped projections of cellular stroma covered by epithelium projected into gland spaces, converting them into slitlike cavities. In these cellular areas the nuclei of the spindle-shaped cells were small and dark staining, while in the less cellular, myxoma-like areas the nuclei were pale and contained a dark nucleolus in a thin network of chromatin. In the latter regions many of the cells contained large vacuoles, and there were spaces containing no stainable material separating the collagen fibers and cells. Capillaries lay scattered throughout the dense cellular areas in moderate numbers, but relatively few could be found in the myxoma-like regions. Mallory stains revealed that the collagen was most dense and arranged more truly in fibers in

the regions containing the spindle-shaped cells with small hyperchromatic nuclei. In the myxoma-like areas the collagen bundles were swollen and less abundant. No mitotic figures were present in any of the various regions. Numerous areas



Fig. 3.—Low power magnification of a microscopic section showing the intracanalicular character of the growth; $\times 25$.

of hemorrhage and necrosis were scattered throughout the tumor, but the evidence of inflammatory reaction was found in those portions of the mass adjacent to the site of the first operation.

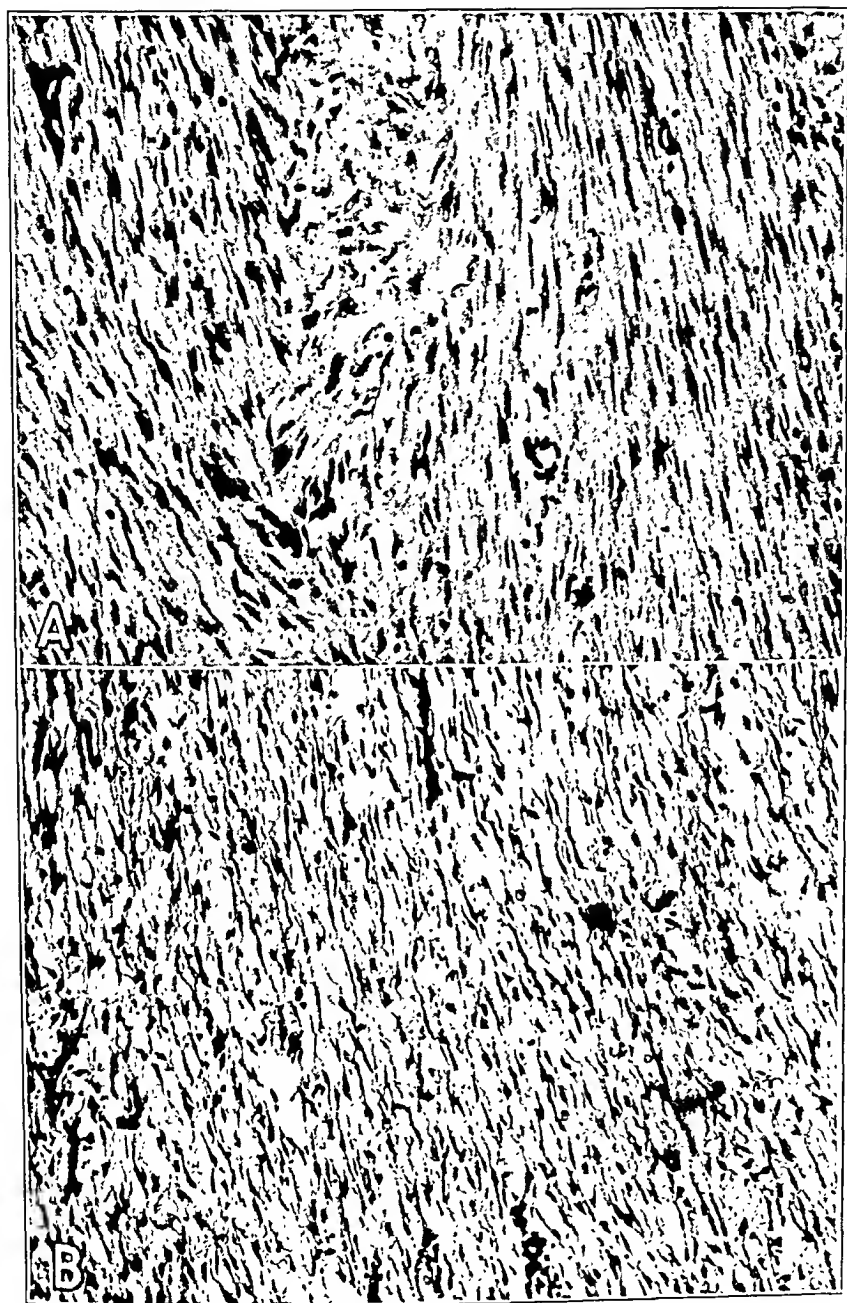


Fig. 4.—*A*, high power magnification of section from the dense cellular zone; $\times 250$. *B*, section from the edematous area; $\times 140$.

COMMENT

The confusion regarding the character of this peculiar mammary tumor is obvious both from the multiplicity of names it has received and from the variations in histologic structure. The extreme cellularity of parts of the tumor suggests a sarcoma. However, the cell-rich stroma is of a benign type, and while sarcomatous degeneration may occasionally result, this is essentially a benign neoplasm. The myxoma-like character of large portions of the stroma has led many observers to classify this tumor as a myxoma or myxofibroma. However, similar areas are often seen in other fibromatous tumors, such as the fibroids of the uterus and the ordinary fibroadenomas of the breast. It seems more likely, as Ochsner³⁴ emphasized, that these "myxomas" merely represent regions of marked edema. Since the general structure is essentially that of an intracanalicular fibroadenoma of the breast, the most fitting name for this tumor would seem to be "giant intracanalicular fibroadenoma of the breast."

SUMMARY

A brief review of the history of the breast tumor commonly known as "cystosarcoma phyllodes" is presented, and its gross and microscopic features are detailed. The 121 cases reported since 1931 are summarized, and our own case is presented. With the 109 cases discussed by Lee and Pack in 1931, the total reaches 122 cases. A list of the various names applied to the tumor is given. Because of the multiplicity of terms used for this pathologic entity, a plea is made for the acceptance of the simple descriptive term, "giant intracanalicular fibroadenoma of the breast."

34. Ochsner, A. J.: *Surgical Diagnosis and Treatment*, Philadelphia, Lea & Febiger, 1920, vol. 2, p. 167.

ADENOCARCINOMA OF TONGUE ARISING FROM VESTIGE OF MEDIAN ANLAGE OF THYROID GLAND

REPORT OF A CASE

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AND

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The origin of the median anlage of the thyroid gland as a diverticulum from the mesobranchial region of the pharyngeal floor, which lies between the ventral extremities of the first two gill pouches, was conclusively demonstrated by Norris¹ in a study of human embryos. According to Joll,² maldevelopment of the median anlage is known to give rise to a variety of abnormalities, which may be located in the midline from the foramen caecum to the level of the suprasternal notch. They include solid tumors, cysts, sinuses and fistulas. A solid tumor of the thyroglossal tract is most common in the region of the foramen caecum, although microscopic amounts of thyroid tissue may occur in any part of the primitive tract. Such a tumor usually consists of well differentiated thyroid tissue and constitutes a lingual thyroid. Ray³ collected 250 cases of this condition recorded in the literature from 1866 to 1938. In the majority of instances in which histologic study was made the structure of this aberrant tissue was similar to that of the normal gland. In a small percentage the fetal pattern of thyroid tissue was found. Cystic changes were not uncommon, being especially prominent in large lingual glands in cretins.

Malignant tumors of the tongue, whose histogenesis seems to represent an abnormal development of the median anlage of the thyroid gland, have been reported. Ray,⁴ in 1918, recorded the case of a man 74

From the Department of Pathology, Vanderbilt University School of Medicine, and from the Protestant Hospital.

1. Norris, E. H.: The Early Morphogenesis of the Human Thyroid Gland, *Am. J. Anat.* **20**:411, 1918.

2. Joll, C. A.: Diseases of the Thyroid Gland, London, William Heinemann, 1932, p. 124.

3. Ray, B. S.: Lingual Thyroid, *Arch. Surg.* **37**:316 (Aug.) 1933.

4. Ray, H. M.: Carcinomatous Transformation of a Lingual Goiter, *Proc. New York Path. Soc.* **18**:12, 1918.

years of age who complained of a gradually enlarging tumor of the tongue which had been present for three years. He had lost 70 pounds (32 Kg.) of weight and was markedly emaciated. On the left side of the tongue there was a "lemon-sized" tumor; this was enucleated, and the patient died two days later of bronchopneumonia. Gross examination of the surgical specimen showed an encapsulated, spherical mass, 5 cm. in diameter. Histologic study revealed that the tumor consisted chiefly of acini of varied size and configuration. These were separated by scanty connective tissue and lined by epithelium of both cuboidal and high columnar type. Papillary projections were noted in some of the acini. "The basement membrane in some areas was not intact and there were definite indications of carcinomatous transformation." A hemorrhagic exudate was found in some of the acini and homogeneous pinkish-staining material in others. A diagnosis of carcinomatous transformation of a lingual goiter was made.

The case reported by Tyler⁵ in 1923 was that of a man who noticed a nodule on the base of the tongue twelve years before death. During the last two years of life he was treated with roentgen rays and radium. A biopsy of the nodule showed thyroid tissue with hyperplasia. At autopsy an ulcerated lesion, 3 cm. in diameter, involving the posterior half of the tongue was seen. Multiple nodules, 1 mm. to 10 cm. in diameter, were found throughout the lungs. There were enlarged lymph nodes along the spine and in the mediastinum. No microscopic studies of the nodules in the lungs or of the lymph nodes were made. The only histologic section described was that from the tongue and consisted of hyperplastic thyroid tissue. A diagnosis of aberrant thyroid gland in the root of the tongue with malignant degeneration was made.

Ashurst and White,⁶ in 1925, recorded the case of a white man 56 years of age who had had a nodule on the base of the tongue for more than twenty years. Seven years after its first appearance the nodule was excised. The mass gradually returned, and the development of the nodules in the neck was noted. Difficulty in swallowing and pain in the tongue also developed. The mass was 8 cm. long and was elevated about 2.5 cm. above the surface of the right side of the posterior half of the tongue. The lymph nodes of the neck were enlarged markedly, and there was moderate enlargement of the epitrochlear, femoral, inguinal and iliac lymph nodes bilaterally. The tumor was partially excised. After this the cervical nodes decreased in size. The patient was observed for several months and continued to do well. Microscopic sections of

5. Tyler, A. F.: Carcinoma of Lingual Thyroid with Metastasis in Lungs. *J. Radiol.* 4:381, 1923.

6. Ashurst, A. P. C., and White, C. Y.: Carcinoma in Aberrant Thyroid Tissue at Base of Tongue, *J. A. M. A.* 85:1219 (Oct. 17) 1925.

the tumor showed areas of typical thyroid tissue. In other areas anaplastic features consisting of cords and alveolar arrangements of the cells were present. In some areas there was little stroma, while in others dense masses of fibrous tissue separating small nests of cells were seen. A diagnosis of adenocarcinoma of the lingual thyroid was made. No microscopic studies of the enlarged lymph nodes were reported.

Levi and Hankins⁷ in 1935 reported a case of carcinoma of the lingual thyroid occurring in a 21 year old white woman who five days previous to examination had noticed a tumor mass at the base of the tongue. In the region of the foramen caecum a reddish brown mass of firm consistency, measuring 2 by 2 by 1.5 cm., was found. It was attached to the musculature of the tongue by a broad base. The tumor was widely excised. Three months later signs of myxedema developed with a basal metabolic rate of -130 per cent. Nine months after operation no evidence of recurrence of the growth had appeared. Microscopic sections showed highly irregular and poorly formed acini of the thyroid type with occasional small amounts of colloid in their lumens. The acinar cells were large, ovoid and spherical, often deeply staining, with occasional poorly formed mitotic figures. The fibrous capsule and the musculature of the tongue were extensively invaded by neoplastic cells. A diagnosis of low grade carcinoma occurring in the thyroid tissue was made.

In 1935 Marchal, Soulié, Grupper and Roy⁸ reported the case of a white man aged 59 who had a hemorrhagic cauliflower-like tumor at the right lateral border of the posterior portion of the tongue and enlargement of the submaxillary lymph nodes. After the removal of the tumor a mass developed in the right biceps muscle. Two years after removal of the tumor of the muscle it recurred. At this time signs of congestive heart failure developed, and the patient died. Autopsy revealed that the tumor of the tongue had recurred and that the cervical lymph nodes were enlarged. A hemothorax was present on the right, and the right pleural surfaces were covered with tumor nodules. A mass of tumor was found replacing the superior pole of the right kidney. The tumor in the right biceps muscle was associated with an arteriovenous aneurysm of the right brachial artery and vein. Microscopic study of all the tumor nodules showed a similar picture. They consisted of acini of varying sizes, some of which were filled with colloid. In other areas the cells were arranged in cords and had a pleomorphic appearance. A few mitotic figures were seen. Definite infiltration of the muscle of the

7. Levi, L. M., and Hankins, F. D.: Carcinoma of Lingual Thyroid, *Am. J. Cancer* **23**:328, 1935.

8. Marchal, G.; Soulié, P.; Grupper, C., and Roy, A.: Adénocancer d'un vestige thyroïdien de la langue. Métastases multiples avec anévrisme artério-veineux de l'humérale, *Bull. et mém. Soc. méd. d. hôp. de Paris* **51**:953, 1935.

tongue was described. A diagnosis of adenocarcinoma of an aberrant thyroid of the tongue was made.

Watson and Pool⁹ stated that in 3 of a series of 167 cases of cancer of the thyroid the growth occurred in lingual thyroid tissue. No details of the clinical or pathologic records of these cases is given.

The condition in the following case report seems to belong to this group of infrequent malignant tumors of the tongue which appear to concern an abnormal development of the median anlage of the thyroid gland.

REPORT OF CASE

History.—A. E. C., a 52 year old white woman, a housewife, was admitted to the Protestant Hospital on Jan. 1, 1941. She was in a semicomatose state. Members of her family stated that about four and one-half years previously the patient had noticed a mass on the posterior surface of the tongue which had gradually increased in size and caused difficulty in swallowing. During the previous four years the lesion had been treated with roentgen rays and radium. The treatment had caused a temporary decrease in the size of the mass, and her ability to swallow had improved. During the last few months before admission, however, swallowing had become almost impossible and she lost 30 to 40 pounds (14 to 18 Kg.) in weight. For two weeks before admission the patient had seemed to have fever and had gradually become stuporous. The past history revealed nothing of significance.

Physical Examination.—The patient was markedly emaciated and stuporous and appeared to be about 60 years of age. Other than evidence of marked loss of weight, the important physical findings were limited to the mouth, pharynx, neck and chest. The mucous membranes of the anterior portion of the mouth showed no lesion. On the dorsum of the posterior half of the tongue there was an elevated hard nodular mass that almost completely filled the posterior part of the pharynx. The surface of this mass was irregular and grayish. No ulcerated areas were seen. The skin of the neck was brownish, and all the underlying tissues were of a firm consistency. No definite nodules could be made out in the neck, and the thyroid could not be felt. The breasts were atrophic. The respiratory movements were shallow and rapid. There was dulness over the bases of the lungs posteriorly, and numerous fine and coarse rales were heard over these areas. The heart was not enlarged, and no murmurs were heard. No abnormalities of the abdomen or of the pelvis were found.

Laboratory Data.—The urine was normal. A white blood count of 5,750 was differentially normal. The hemoglobin content was 12.5 Gm. per hundred cubic centimeters.

Course in Hospital.—The temperature rose from 100 to 101.2 F. as the patient gradually passed into complete coma. The blood pressure fell from 128 systolic and 80 diastolic to 50 systolic and 40 diastolic. She was treated with intravenous fluids and with ephedrine but failed to respond; she died eighteen hours after admission.

9. Watson, W. L., and Pool, J. L.: Cancer of the Thyroid. *Surg., Gynec. & Obst.* 70:1036, 1940.

Postmortem Examination.—Autopsy was performed one hour and forty minutes after death. The skin generally was dry and inelastic, and the skin of the neck was firmly attached to the underlying tissue.

The peritoneal cavity contained no free fluid, and its surfaces were free of exudate. No free fluid was present in the pleural cavities. The pleural surfaces of

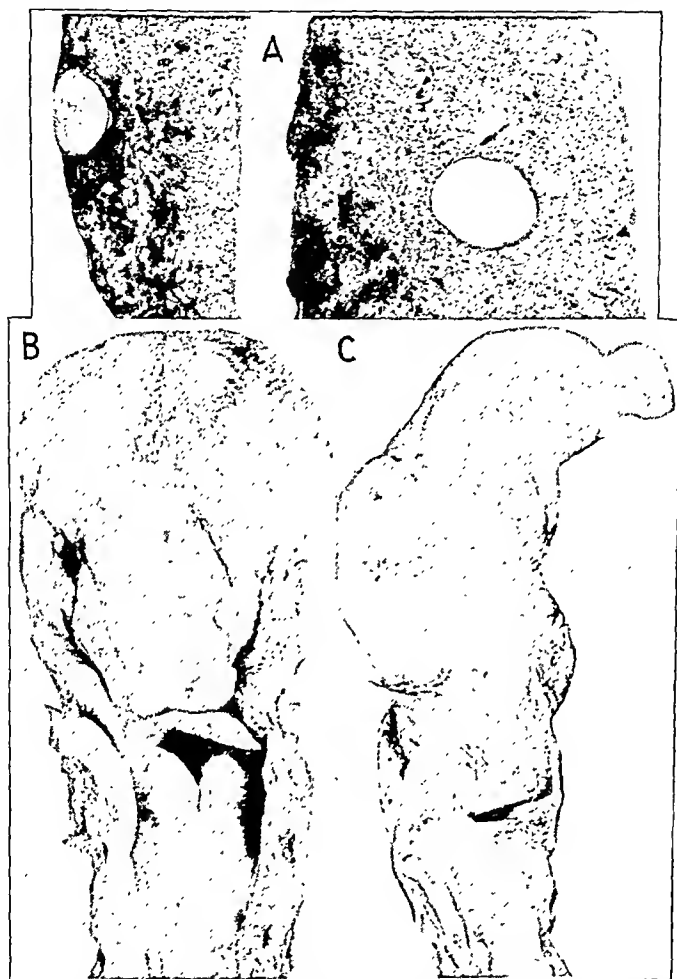


Fig. 1.—*A*, the cut surface of two portions of lung tissue showing metastatic tumor tissue. *B*, superior view of the tongue and larynx. *C*, sagittal section of the tongue and larynx.

the lower lobe and the interlobal fissures of the right lung were covered with a fibrinous exudate. The heart showed no gross lesions. The left lung weighed 460 Gm. and the right lung 600 Gm. The lower lobes and the inferior portion of the upper lobes of the two lungs and the middle lobe of the right lung were generally of a firm consistency. The small bronchi appeared dilated and stood out

distinctly on the cut surface. In each lobe of the right lung and in the lower lobe of the left lung several firm discrete nodules, which measured from 0.5 to 2 cm. in diameter, were found (fig. 1 *A*). On section these nodules consisted of homogeneous grayish white tissue which was mottled in some areas by reddish discolorations. No gross evidence of tumor metastasis was seen in the tracheobronchial lymph nodes.

The gastrointestinal tract, liver, spleen, pancreas, adrenals, kidneys, ureters, bladder and internal genitalia showed no gross lesions.

The organs of the neck, including the tongue, were removed. From the surface of the posterior half of the tongue a grayish white hard lobulated nodule of tissue protruded. The surface of this measured 4 by 2.5 cm. It projected approximately 1.5 cm. above the surface of the tongue. The surface of the mass was not ulcerated. The mass filled the space between the root of the tongue and the epiglottis and displaced the epiglottis posteriorly and inferiorly (fig. 1 *B*). A sagittal section through the tongue and pharynx showed replacement of the posterior half of the genioglossus and genioid muscles and the tissue between the epiglottis and these muscles by tumor tissue (fig. 1 *C*). Extension of the tumor into the tissues inferior and lateral to the tongue could not be made out grossly. The tissue of the pharyngoepiglottic folds and the aryepiglottic folds appeared edematous, and the superior aperture of the larynx was narrowed. An oval superficial erosion of the mucosa, which measured 0.4 by 1 cm., was noted on the first portion of the esophagus. No other lesions of the esophagus were seen. No enlarged cervical lymph nodes were found. The subcutaneous tissue of the anterior and lateral portions of the neck was indurated, apparently from an increase in fibrous tissue. The thyroid gland was small, weighing only 7.5 Gm.

Microscopic Examination.—Blocks of tissue were fixed in Zenker's fluid with 10 per cent acetic acid, and sections were stained with hematoxylin and eosin. Sections of the heart, gastrointestinal tract, liver, spleen, pancreas, kidneys and bladder showed no remarkable microscopic changes.

Sections of the tongue showed no ulceration of the mucous membrane. In some areas the tumor tissue was found adjacent to the mucous membrane, but no definite invasion of the epithelium was seen. The stroma adjacent to the epithelium was filled by monocytes and lymphocytes. Large areas of muscle had been completely replaced by tumor tissue, and in other areas the muscle had been infiltrated by the neoplastic cells. The tumor tissue consisted chiefly of irregularly shaped masses of cells with indistinct cell boundaries. The cytoplasm stained lightly. The nuclei were relatively large and ovoid and contained small scattered masses of chromatin. No mitotic figures were seen. These masses of cells were separated by a loose fibrous tissue stroma. Scattered throughout these groups of cells acini of varying sizes were seen. A few of the acini were lined by a single layer of cuboidal or columnar epithelial cells which showed a uniform polarity. Others were lined by several layers of cells which were irregular in shape. In the lumen of a small proportion of the acini there was a homogeneous pink-staining material. The majority contained pale pink-staining granular material (fig. 2, *A* and *B*).

The metastatic nodules in the lungs presented a microscopic picture similar to that of the tumor of the tongue (fig. 2, *C* and *D*). Evidence of bronchiectasis, etc.

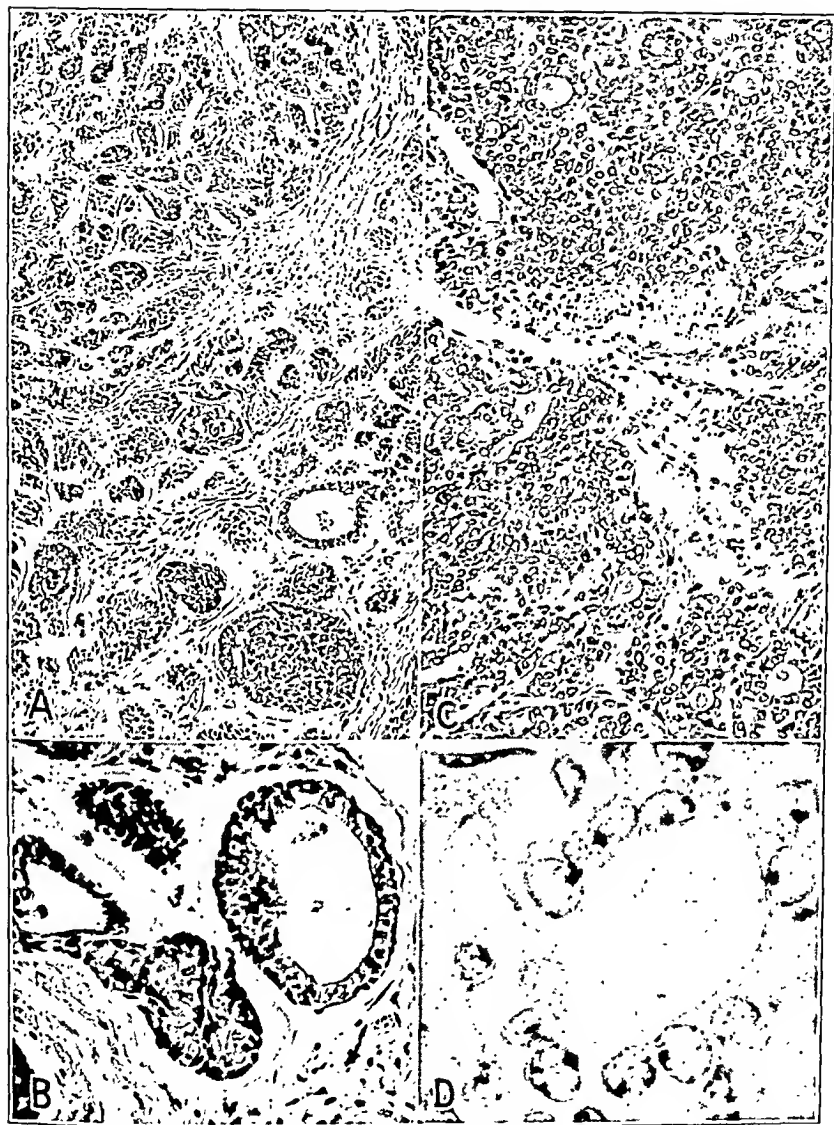


Fig. 2.—Photomicrographs (hematoxylin and eosin stains) showing (*A*, $\times 100$) and (*B*, $\times 250$) tumor of the tongue and (*C*, $\times 160$ and *D*, $\times 1,160$) metastatic tumor of the lung.

scopic abscesses and bronchopneumonia which was undergoing organization was also present in the sections of the lungs.

Sections of the thyroid gland showed large and small acini filled with colloid. The large acini were lined by flat epithelium and the smaller acini by cuboidal epithelium. The acini were widely separated by loose connective tissue, indicating atrophy or hypoplasia of this gland. Sections of the tracheobronchial lymph nodes showed acute and chronic lymphadenitis with no evidence of metastatic neoplastic lesions.

Diagnosis.—A diagnosis of the following conditions was made: adenocarcinoma of the tongue arising from a vestige of the median anlage of the thyroid gland with metastasis to the lungs, bronchiectasis, multiple microscopic abscesses of the lungs, organizing bronchopneumonia and hypoplasia of the thyroid gland.

COMMENT

The primary site of the tumor in the case presented suggested that its origin might represent an abnormal development of the median anlage of the thyroid gland. This idea was supported by the histologic structure of the neoplasm. It did not have the characteristics of an anaplastic carcinoma but appeared to be embryonic glandular tissue. The histologic structure corresponded closely to that of the thyroid tissue found in 50 mm. human embryos (Norris¹⁰). The fact that embryonic glandular tissue may persist along the thyroglossal tract is illustrated by a case reported by Marshall.¹¹ In describing the central portion of the thyroglossal tract in his case, he stated: "The whole structure gives the idea of embryonic or imperfectly developed glandular tissue." In the case presented there seemed to be a persistence of embryonic glandular tissue in the region of the foramen caecum in which malignant neoplastic qualities developed while the histologic structure of embryonic glandular tissue was maintained. The malignant qualities were evidenced by invasion of the musculature of the tongue and by the metastatic lesions in the lungs. No well differentiated thyroid tissue was found in the tongue. This neoplasm did not appear to represent a carcinoma of a lingual thyroid but seemed to have its origin in a vestige of the median anlage of the thyroid which had not differentiated to the adult type of thyroid tissue.

The infrequency of carcinoma of the tongue which arises either from lingual thyroid or from an undifferentiated vestige of the median anlage of the thyroid gland is indicated by the few cases which have been recorded in the literature. In some of these cases inadequate evidence is presented to support the diagnosis made. In Tyler's report¹² the only

10. Norris, E. H.: The Mesodermogenesis of the Follicles in the Human Thyroid Gland, *Am. J. Anat.* **20**:411, 1916.

11. Marshall, C. F.: The Thyro-Glossal Duct or Canal of Man, *J. Anat. & Physiol.* **26**:94, 1891.

microscopic sections described were from the tongue and showed hyperplastic thyroid tissue. No morphologic evidence that the tumor of the tongue was malignant or that the lesions in the lungs and lymph nodes represented metastatic tumor tissue from the tongue was presented. In Ray's case⁴ the diagnosis of a carcinomatous transformation of a lingual goiter was made. Grossly the tumor removed from the tongue was encapsulated. Microscopically the tumor seemed to consist chiefly of thyroid tissue which was hyperplastic, as evidenced by the papillary projection of epithelium into the acini. He stated that "the basement membrane in some areas was not intact and there were definite indications of carcinomatous transformation." He did not elaborate further on the evidence of malignancy. No invasion of the musculature of the tongue was described, and no metastatic lesions were demonstrated.

In the case reported by Ashurst and White⁶ the portion of the tumor studied microscopically was that which projected above the surface of the tongue; this showed typical thyroid tissue in areas. "In certain areas of the section, running from typical lobules of thyroid tissue, were dense accumulations of epithelial cells, placed in bands or cords; and in still other areas there was a tendency to alveolar arrangement, that is, an arrangement typical of adenocarcinoma. . . . In other parts this carcinomatous arrangement was marked by increase of fibrous tissue, separating the epithelial cells into distinct cancer nests, with somewhat the appearance of scirrhus carcinoma." No definite evidence of local invasion or of metastasis was described. The presence of epithelial cells in thyroid tissue arranged in bands and in alveolar form is not conclusive evidence of malignancy. Levi and Hankins⁷ presented decisive evidence to support their diagnosis of carcinoma of lingual thyroid in their case. The development of the clinical picture of myxedema in the patient three months after operation indicates that the tumor was a lingual thyroid. The microscopic evidence of malignancy, including invasion of the capsule and of the musculature of the tongue by anaplastic tumor tissue, seems to be conclusive.

The microscopic structure and the multiple metastases confirmed the diagnosis of an adenocarcinoma of a thyroid vestige of the tongue in the case reported by Marchal, Soulié, Grupper and Roy.⁸ There was well differentiated thyroid tissue present in the tongue, as well as the anaplastic malignant tissue.

The lesion in the case we have described seems to be this kind of tumor in that it is an adenocarcinoma of the tongue that arises from a vestige of the median anlage of the thyroid gland. It differs from the growths in the other reported cases in that the vestige of tissue had not differentiated into the adult type of thyroid tissue but had remained embryonic in structure.

Conclusions cannot be drawn as to the natural history of this group of neoplasms from the few cases which have been reported. Apparently the possibility of malignancy should be considered in a patient presenting a tumor in the region of the foramen caecum. There is some evidence that surgical excision is the treatment of choice.

SUMMARY

1. A case of adenocarcinoma of the tongue whose histogenesis seemed to concern the persistence of a vestige of the median anlage of the thyroid gland is reported.

2. In this case the vestige of tissue maintained its embryonic structure, invaded the musculature of the tongue and metastasized to the lungs.

3. Other cases of adenocarcinoma of the base of the tongue in which the origin seemed to concern an abnormal development of the median anlage of the thyroid gland are reviewed.

CREMASTERIC SPASM

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PHILADELPHIA

The cremaster muscle, originating from the lower fibers of the obliquus internus and transversalis muscles of the abdomen, runs along the spermatic cord and then spreads fanwise downward within the cremasteric fascia to envelop the testis and adnexa. The size of these muscle strands varies from 20 to 200 microns in the normal person. The response of the cremaster to stimuli is the same as that of any other striated muscle. It is lowered in atrophy and increased in hypertrophy.

I encountered a case of bilateral hypertrophy of the cremaster muscle with spasticity, causing painful contractions and thus disrupting the patient's daily work. These painful spasms finally became unbearable, and the patient was forced to seek relief through operation:

REPORT OF A CASE

C. R., a white man 24 years of age, was referred by Dr. N. Pastor to the Mount Sinai Hospital and admitted Nov. 7, 1940. His occupation was that of a shipper. His chief complaint was, "The inside of the scrotum swells up tight." This condition started about three months previously. While working at his job, without apparent reason, he would suddenly feel both testes pulling upward in a painful spastic contraction and remaining high, held in place by a tense scrotum pressed tightly against the pubic bone (fig. 1). He would then stop working, as any movement would aggravate the painful spasm. He had to lie down and rest until the spasm wore off. Lately, these spasms had begun to occur more frequently. He had lost 9 pounds (4 Kg.) in three months, worrying over his condition. He had always been in good health and had had no operations. His sexual history was normal until three months before admission, and then each attempt would bring on painful spasms.

Physical examination disclosed nothing to account for his symptoms. The internal and external genitalia were normal. The cremaster reflex was hyperactive on both sides. The spasm could not be brought on by local irritation. The blood and urine were normal.

Operation.—On November 7, under low spinal anesthesia, a bilateral operation on the scrotum was performed. An incision was made in the upper part of the scrotum down to the cremasteric fascia. The spermatic cord and testis were lifted out of the scrotum by blunt stripping. The muscle bundles of the cremaster were distinctly overdeveloped with heavy strands of cremaster muscle running fanwise over the fascia downward. It was noted that the slightest pinch with the forceps would cause a contraction with a resulting upward pull of the testis. The

cremasteric fascia was then incised all around the spermatic cord and stripped clean off the cord and testis. Thus the entire cremasteric fascia was removed. The testis was then replaced in the scrotum, and the skin was closed with clips around a small piece of rubber dam drainage. The same findings were noted, and the same procedure was carried out on the opposite side.

Pathologic Observations.—Two pieces of cremasteric fascia, measuring 9 by 1 cm. and 7 by 5 cm., respectively, were removed. They appeared normal except for tremendous hypertrophy of the cremasteric muscle bundles (fig. 2).

LITERATURE

Reviewing the literature, one finds only a few reports of similar cases (Mitchell,¹ Hamburger,² Cornil and Mosinger,³ Zucarelli,⁴ Talmud,⁵ Haberland,⁶ Thomas,⁷ Kovalevsky⁸ and McDonald and Mayo⁹).

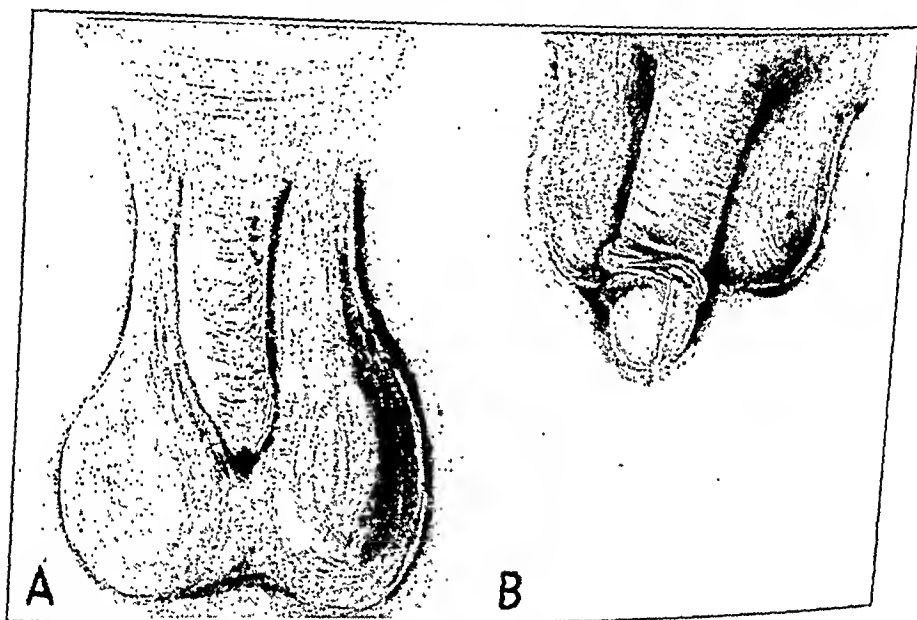


Fig. 1.—*A*, position of testes at rest; *B*, during spasm. Note upward and inward pull.

CAUSATION

The explanation of the cremasteric spasm is still obscure. Two theories have been advanced. One group of authors expressed the

1. Mitchell, S. W.: *J. Nerv. & Ment. Dis.* 4:577, 1879.
2. Hamburger, F.: *München. med. Wchnschr.* 66:461, 1919.
3. Cornil, L., and Mosinger, M.: *Paris méd.* 2:308, 1930.
4. Zucarelli, P., cited by Cornil and Mosinger.³
5. Talmud, J. L.: *Ztschr. f. d. ges. Neurol. u. Psychiat.* 118:414, 1929.
6. Haberland, H. F. O.: (a) *Arch. f. klin. Chir.* 162:660, 1930; (b) *Ztschr. f. Sexualwissensch.* 17:191, 1930.
7. Thomas, A.: *Paris méd.* 2:73, 1927.
8. Kovalevsky, P. J.: *Rev. neurol.* 2:164, 1925.
9. McDonald, J. R., and Mayo, C. W.: *Atrophy of Cremaster Muscle. Arch. Path.* 28:141 (Aug.) 1939; *Minnesota Med.* 22:540, 1939.

opinion that the spasms are due to psychogenic influences and originate in the sexual life of the person, thus precluding a neurasthenic background (Hamburger²). The second theory was advanced by those authors who saw spasms of the cremaster muscle occur in patients with local or central brain or spinal injuries (Cornil and Mosinger³ and

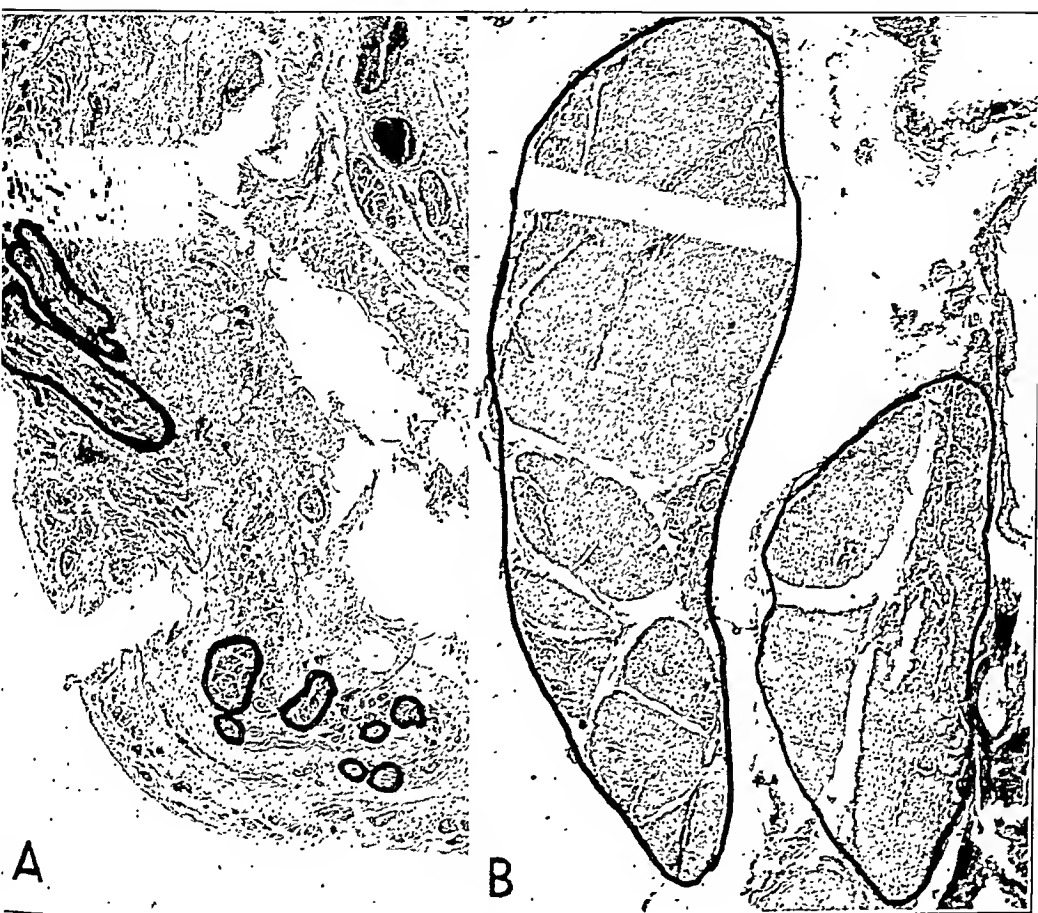


Fig. 2.—*A*, histologic picture of the normal cremasteric fascia; *B*, of the hypertrophied one. Both are magnified thirty-two times. Bundles outlined in black. Actual measurements show the hypertrophied bundles to be twenty-five times larger than normal.

Zucarelli⁴). Zucarelli saw spasms of the cremaster muscle develop in a man after a brain injury in 1 case and after a bullet wound in the thigh in another. A third theory must be sought by those authors who observed spasms of the cremaster muscle in persons free from nervous disturbances and definitely known to be of an opposite mentality, with no local or

central injury. No cause could be found to which one might attribute the origin of the spasms in these patients. In many, the exciting occasion was not sexual at all. In 1 case, the testis would move up and down with each respiration (Kovalevsky⁸). In my case the spasms occurred in a hard working factory worker, mostly during working hours, after he had been on his feet for a number of hours. Haberland⁶ analyzed the mental state of his 7 patients and found that only 2 could be classified as neurasthenic; the other 5 had absolutely no symptoms of neurasthenia.

The spasms occur mostly at night and at times of sexual excitement but will also occur during the waking hours. In some instances, stroking of the thighs or a stimulus to the lower parts of the body will elicit a spasm.

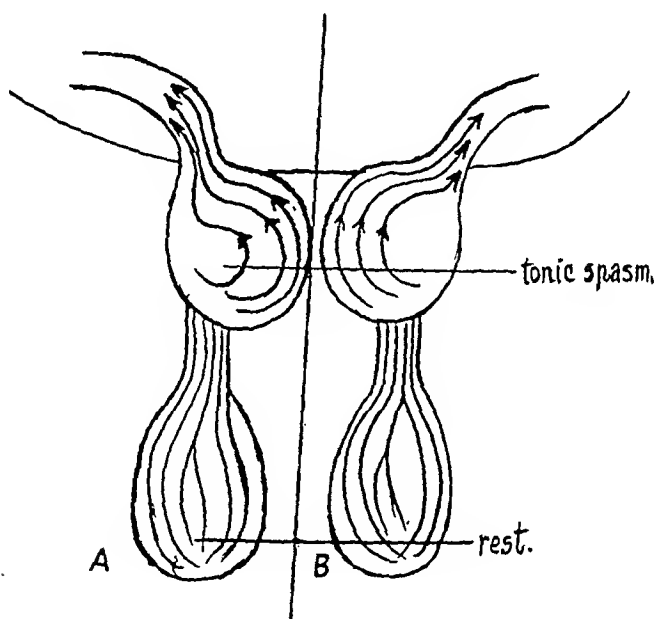


Fig. 3.—Upward pull and inward rotation of testes during tonic spasm as compared with their position at rest (schematic).

SYMPTOMS

The main complaint, which brings the patient to the physician, is pain of varied degree. The character and degree of the pain depend on the type of spasm in the individual case. In clonic spasm the pain is sharp and radiates upward into the loin but lasts only as long as the spasm, usually ten to twelve minutes. These cases are rare. In the majority of the cases observed the spasm is tonic. The pain is not as severe as in the clonic type but lasts longer and, because of the frequent recurrence, becomes annoying. In my case, the spasm had the character of a tetanic contraction; both testes were pulled upward and inward and kept in this position of painful compression for several hours (fig. 3). The only way the patient could stop the spasm was to lie down; the spasm would then gradually quieten. On several occasions he had to stop working

for an entire day. In most other cases reported, the pain occurred during the night and would cause sleeplessness. In others, the spasms were brought on by the slightest sexual irritation and, because of the extreme pain, made coitus impossible.

The history varies from several weeks to several years. My patient gave a history of three months; others reported three years and over (Haberland ⁶ and McDonald and Mayo ⁹).

PATHOLOGIC FACTORS

An extensive study of the cremaster muscle was undertaken by McDonald and Mayo,⁹ who examined 80 specimens obtained at autopsies and at operations. In 9 instances, they found the cremaster muscle normal. In 42, the muscle showed atrophy. In 29, the muscle was infiltrated with lymphocytes. In none did they find hypertrophy of the muscle. They observed hypertrophy of the muscle only in their

Comparative Measurements of the Muscle Bundles of Normal Cremaster Muscles and a Cremaster Muscle with Hypertrophy

Patient from Whom Obtained	Condition of Cremaster Muscle	Age, (Yr.)	Disease	Length of Muscle Bundles (Microns)
1.....	Normal	22	Emaciation	20 to 60
2.....	Normal	54	Pneumonia	40 to 80
3.....	Normal	30	Accident	60 to 200
4.....	Spastic	24	Operation	1,700 to 2,600

reported operative case. This single instance of hypertrophy in 80 cases indicates the extreme rarity of the condition and explains why cremasteric spasm is seen in the clinic in only a few cases. In my case, there was tremendous hypertrophy of the muscle. In order to determine the degree of hypertrophy, a comparison with normal cremaster muscles was made. The size of the muscle bundles was measured under the microscope, with the aid of a ruled ocular. The table shows the results of this study.

The average muscle bundle measures about 120 microns. In my case, the muscle attained a remarkable degree of hypertrophy, measuring up to 2,600 microns.

TREATMENT

Several forms of treatment have been suggested by various authors. The same therapeutic procedure gave opposite results in the hands of different men. Drug therapy combined with psychotherapy was advocated by Hamburger.² He expressed the belief that neurasthenia is the underlying cause of the spasms. Treatment, therefore, should aim to reduce the irritability of what he called an exaggerated cremasteric reflex.

This regimen, however, has not been of value in the experience of other investigators. Section of the spermatic nerves was tried by Haberland⁴ without effect, while Talmud⁵ claimed to have obtained a permanent cure by this procedure. Excision of the inguinal nerves by Haberland gave only temporary relief. He noted similar temporary improvement, lasting two weeks, after spinal anesthesia. He also tried injections of an estrogen and observed only slight temporary improvement. Partial excision of the cremasteric fascia around the spermatic cord gave no results in Haberland's case, while in the case of McDonald and Mayo⁹ it resulted in complete cure. Haberland, who reported the largest series of personal cases,^{6b} claimed that best results were obtained with hot sitz baths and diathermy.

There is no report in the literature of the complete bilateral removal of the cremasteric fascia, as carried out in the case herein reported. A complete and permanent cure was obtained. Follow-up examination showed complete absence of any scarring or induration of the scrotal contents on either side. The cremasteric reflex, as one would expect, was completely absent on both sides. There was great improvement in the patient's general condition, both mental and physical. He regained the weight lost during the three months previous to the operation, and his mental outlook returned to normal. He pursued his daily work with vigor, unhindered by any sensation in either side of the scrotum.

STAINLESS STEEL AND VITALLIUM IN INTERNAL FIXATION OF BONE

A COMPARISON

J. ALBERT KEY, M.D.

ST. LOUIS

The earlier work on the internal fixation of bone was done with corrosive metals, because suitable noncorrosive metals were not available. For the most part, surgeons emphasized aseptic technic and adequate mechanical fixation as the important factors in determining the success or the failure of an operation. For instance, Groves,¹ as a result of 100 experiments on animals, concluded that ordinary steel plates were well tolerated by the tissues and that long plates fixed with cotter pins were more efficient than short plates fixed with screws, because the screws soon became loose when subjected to mechanical force and caused the fixation to fail before union occurred.

There was, however, some interest in the reaction of tissues to various metals, and von Baeyer,² in 1908, in an extensive monograph described the cellular reaction around pieces of metal which were left buried in the tissues for varying periods. The metallic particles set free by corrosion were identified in the surrounding tissues, and the cellular reactions were described in detail. He also noted that when two different metals, copper and zinc, were implanted close together rhythmic contraction occurred in the underlying muscles and the connective tissue cells were arranged in the direction of the electric current. In a second paper von Baeyer³ noted that when small rolls of zinc and copper were placed beneath the skin of a rabbit and left for several months the copper remained shiny instead of corroding, the copper ions migrated toward and united with the zinc instead of becoming oxidized or dissolved and the copper was no longer poisonous to the cells. He stated that the general phenomenon of electrolysis occurred with other metals, such as

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1. Groves, E. W. H.: An Experimental Study of the Operative Treatment of Fractures, *Brit. J. Surg.* 1:438, 1913.

2. von Baeyer, H.: Foreign Bodies in the Tissues, *Beitr. z. klin. Chir.* 58:1, 1908.

3. von Baeyer, H.: The Relation of Metallic Zinc and Copper in the Tissues, *München. med. Wchnschr.* 56:2416, 1909.

steel and copper and caused the iron to rust quickly and that before advantage could be taken of the electrolytic processes in surgical procedures the various combinations of metals would have to be studied further.

Zierold ⁴ studied the reaction of bone to various metals and noted that it was indifferent to the implantation of some metals and sensitive to the introduction of others. The metals of the first type were found to be unchanged after having been buried in the tissues for some time, but those of the second type exhibited evidence of varying degrees of corrosion. He stated that in mass form a metal could modify other elements only at the expense of its own substance, that in an electrolyte this was accomplished by the dissociation of metallic ions to the end that a colloidal solution was formed which conformed to the solution pressure of the metal, that this process underlay the phenomenon which is termed corrosion and that this explains the changes which occur in steel and iron when they are exposed to the action of an electrolyte (tissue fluids). It was his conclusion that of the metals studied gold, aluminum and stellite (an alloy of cobalt, chromium and tungsten) were readily tolerated by bone and tended to become encapsulated with but little hindrance to the reparative process. They appeared to be inert and unaffected by the living cells and body fluids. He further noted that steel, which was poorly tolerated and readily soluble, seemed to be the least suitable of all metals for fixation of bone.

Stainless steel was first introduced in surgery as the Krupp steel wire, which was used for bone sutures. Lange ⁵ studied the reactions of the bone and the soft tissues of experimental animals to this wire and compared the results with those of similar experiments performed with wire made of iron and bronze. From microscopic and clinical data he concluded that the Krupp steel wire was the ideal suture material for bone, as it was strong, caused no reaction in the tissues and interfered less with the building of callus than did wire of iron or aluminum bronze.

Jones and Lieberman ⁶ compared the interaction of bone and stainless steel with that of bone and vanadium steel in experimental animals. They emphasized the fact that there was a considerable number of stainless steels on the market and that they varied greatly in composition. They studied nickel-free rustless steel, high nickel rustless steel, low nickel rustless steel and vanadium. The method used was to bury tacks in the bones of experimental animals, leave them for from one to two and one-

4. Zierold, A. A.: Reaction of Bone to Various Metals, *Arch. Surg.* 9:375 (Sept.) 1924.

5. Lange, M.: Krupp Steel Wire as Bone Suture Material, *Ztschr. f. orth. Chir.* 47:520, 1926.

6. Jones, L., and Lieberman, B. A., Jr.: Interaction of Bone and Various Metals, *Arch. Surg.* 32:991 (June) 1936.

half months and then determine their loss in weight; the reaction of the surrounding bone to the metals was also studied. They concluded that the intensity of reaction in the bone was directly proportional to the chemical changes which occurred in the metal with which it was in contact and that such changes might be grouped under the general term corrosion. They expressed the opinion that the high chromium, low nickel rustless steels were the metals of choice, because corrosion in those alloys was minimal, although they were not completely nonirritant in bone.

Haas⁷ also emphasized the fact that stainless steels vary in composition and that some of them corrode relatively quickly. A photograph of a nail of the VM rustless steel which was markedly corroded was reproduced in his paper, and he stated that the V2A steel should be used, as it was about ten times as resistant to corrosion in sea water as was the VM stainless steel.

Orsos⁸ emphasized that an electric current is generated when bone is fixed by two different metals and cited a case in which an aluminum plate was placed on the humerus in close contact with the radial nerve. As soon as the brass screw came in contact with the aluminum plate there was a strong contraction of the muscles, with extension of the hand and fingers. This was due to the electric current generated by the two metals in an electrolyte, as under these conditions they formed a small galvanic element. In Ringer's solution the current amounted to 0.25 milliamperes and gradually decreased after about fourteen hours to 0.08 milliamperes, at which level it remained constant. Orsos expressed the opinion that only a homogeneous metal, with which an electric current could not be formed, should be used, and he recommended employing an autoplasmic bone plate fixed by a single wire to either fragment.

Ménégaux, Moÿse and Odiette⁹ and others studied the influence of metals on the growth of fibroblasts and other cells in tissue cultures. They found that copper, magnesium, aluminum bronze and brass were very toxic. Silver, nickel and chromium were moderately toxic, while gold, V2 extra stainless steel and platinostainless D steel were neutral and had a minimal toxicity. Consequently, metals of the last group were recommended for the internal fixation of bone. They expressed the

7. Haas, W.: "Rustfree" Steel in Surgery, *Arch. f. orthop. u. Unfall-Chir.* **37**:606, 1936.

8. Orsos, E.: The Current Generated by Bone Sutures, *Zentralbl. f. Chir.* **56**:1014, 1925.

9. Ménégaux, G.; Moÿse, P., and Odiette, D.: Growth of Connective Tissues of Bone in Tissue Cultures in the Presence of Certain Metals, *Presse méd.* **42**:658, 1934. Ménégaux, G., and Odiette, D.: Cytotoxic Action of Certain Metals on Human Osteoblasts in Tissue Cultures, *ibid.* **43**:1555, 1935.

opinion that two metals of different nature in association did not have an action different from that of the isolated metals and that the importance of the electrical phenomena created by the association of two metals was negligible as compared with the toxicity of the metal itself. The results of their tissue culture experiments were confirmed by investigation on animals in which the same metals were placed beneath the periosteum. They concluded that the toxicity depended entirely on the metal and that the tissue reacted the same way to a foreign body whether it was *in vitro* or *in vivo*.

Zeinert,¹⁰ on the other hand, emphasized the importance of the electric currents in buried metallic foreign bodies, and to show the influence of such currents he fixed the femurs of rabbits with wires placed in the subcutaneous tissue, according to the method of Magnus. Through one wire a current of 1.5 volts was passed for three seconds daily for eight days. This current caused the wire to corrode, so that the change was similar to that which would have occurred over a period of five months. For this reason he expressed the belief that metals, and he included stainless steels, should be left in the tissues for only a short time.

Perves and Damany¹¹ reported a case in which there were pain and cyanosis in the forearm after fixation of a fracture with a Lambotte plate and the symptoms were relieved by removal of the plate. They expressed the belief that the symptoms were due to the electric current generated and showed that between the Lambotte screws and the plate there was a difference in potential of 66 millivolts, while between Sherman vanadium steel screws and plates the difference was 44 millivolts and between the Sherman screws and the Lambotte plate, such as were present in their patient, the difference was 52 millivolts. They also tested plates of platinostainless steel with screws of similar material and found that the difference in potential was so slight that it was not measurable.

Masmonteil,¹² likewise, cited 3 cases in which there was profound corrosion of screws and the alterations in potential between the corroded and the noncorroded portions of the screws were measured. This difference varied from 0.134 to 0.153 millivolt. He expressed the belief that the electrolytic phenomenon was the prominent factor in causing the unfavorable reaction of bone to the metals used for osteosynthesis, and he recommended that the metals used be inert chemically and physically and isoelectric with the bone (with a potential of about 0.210 millivolt).

10. Zeinert, H.: *Electric Currents in Buried Metallic Foreign Bodies*. Arch. f. orthop. u. Unfall-Chir. **37**:261, 1936.

11. Perves, J., and Damany, G.: *The Importance of the Electrolytic Factor in Osteosynthesis*, Mém. Acad. de chir. **64**:650, 1938.

12. Masmonteil, F.: *The Tolerance of Bone for Metallic Foreign Bodies*. Presse méd. **43**:1915, 1935.

Bothe, Beaton and Davenport¹³ buried tacks of various metals close together in the bones of cats and studied them after periods of from eight to two hundred and thirty-two days. They expressed the opinion that electric potentials were not an infallible guide to the amount of reaction between the bone and the metal, and they suggested that electrolysis is an accompaniment of the unfavorable reaction of the bone rather than the direct cause of it. In their experiment each metal retained its characteristic individuality of reaction in spite of the conditions with regard to electrolysis and the inert alloys and titanium remained inert in the presence of reactive metals.

Hudack¹⁴ reviewed the clinical experience at the Presbyterian Hospital, New York, with high chromium, low nickel stainless steel and also reported the results of experiments on 5 dogs in which the bone plates were left in the tissues for periods varying from two days to two years. After removal the plates and screws were weighed. They showed an average loss in weight of approximately 0.1 per cent. The plates were well tolerated and caused no reaction in the bone. Microscopic section showed that the bone was closely approximated to the metal and had grown into the threads of the screw and remained living. He recommended that all stainless steel material should be passivated before use by immersion in 20 per cent nitric acid at a temperature of 65 C. (149 F.) for a half hour or more. This creates a chromic oxide coating on the steel. He also recommended that the steel be polished before being subjected to the passivating process.

Venable, Stuck and Beach¹⁵ placed screws of vitallium, copper, brass, galvanized iron, vanadium steel, plain steel and chromium-plated and silver-plated copper in the bones of animals and studied the bones and the screws at intervals which varied from a few days to three months.

13. Bothe, M. F.; Beaton, L. E., and Davenport, H. A.: Reaction of Bone to Multiple Metallic Implants, *Surg., Gynec. & Obst.* **71**:598, 1940.

14. Hudack, S.: High Chromium, Low Nickel Steel in the Operative Fixation of Fractures, *Arch. Surg.* **40**:867 (May) 1940.

15. Venable, C. S.; Stuck, W. G., and Beach, A.: The Effects on Bone of the Presence of Metals Based upon Electrolysis: Experimental Study, *Ann. Surg.* **105**:917, 1937. Stuck, W. G.: Electrolytic Destruction of Bone Caused by Metal Fixation Devices, *J. Bone & Joint Surg.* **19**:1077, 1937. Venable, C. S.: Electrolytic Action Between Metals in Bone Surgery, *Arch. Phys. Therapy* **19**:285, 1938; Osteosynthesis in the Presence of Metals: Studies on Electrolysis, *South. M. J.* **31**:501, 1938. Venable, C. S., and Stuck, W. G.: Fractures: Recent Advances in Treatment with Non-Electrolytic Metal Appliances, *J. Indiana M. A.* **31**:335, 1938; Electrolysis Controlling Factor in the Use of Metals in Treating Fractures, *J. A. M. A.* **111**:1349 (Oct. 8) 1938. Venable, C. S.: Application of Neutral Metal in Fractures, *South. Surgeon* **8**:456, 1939. Venable, C. S., and Stuck, W. G.: Vitallium Nails in Fractures of the Hip, *Surg., Gynec. & Obst.* **70**:964, 1940.

They found that screws made of all the metals except vitallium caused reaction and absorption in the bone and became loose. They expressed the opinion that this unfavorable effect on bone was due to electrolysis, which was caused by variation in the local electric resistance of the metals. They deserve great credit for calling the attention of American surgeons to this aspect of the internal fixation of bone. As a result of their observations, vitallium was recommended as the material of choice for the internal fixation of bone.

Since there appears to have been no comparative study of vitallium and the better grades of stainless steel, which are the materials now commonly used for the internal fixation of bone, it seemed worth while to make the present study.

EXPERIMENTAL OBSERVATIONS

In the beginning the standard 18-8 stainless steel was used. This contains 18 to 20 per cent chromium, 8 to 10 per cent nickel, 65 to 70 per cent iron and small amounts of carbon, manganese, silicon, phosphorus and sulfur. This is the steel which is now used by most instrument houses in this country for manufacturing materials, such as screws, plates, wires and nails, which are intended for the internal fixation of bone. About three months ago, I obtained from the Zimmer Manufacturing Company some screws and plates made of a new stainless steel known as enduro, or 18-8 S-MO. This steel contains from 16 to 20 per cent chromium, a maximum of 14 per cent nickel and from 2 to 4 per cent molybdenum. It has been introduced for use in surgical procedures on bone largely through the efforts of Dr. J. A. Carnes, of Massillon, Ohio. I have obtained further supplies of this material and certain data on it from Dr. Carnes.

Animal Experiment 1.—The first experiment consisted of the implantation of a series of nails, plates and screws in the femurs of 6 dogs. Prostheses made of stainless steel were placed in one femur, and similar prostheses made of vitallium were placed in the other femur of each animal. The operations were performed with the animal under general anesthesia, under aseptic conditions. The dogs were maintained for thirteen months and were then killed. Unfortunately, 1 dog was lost; so only the observations on the 5 remaining animals could be used to reach conclusions. Each femur contained six or more pieces of metal. In one instance there was a mild infection in one wound, which caused some excess growth of new bone.

The bones were removed and fixed in solution of formaldehyde at the end of the experiment. A small piece was taken for microscopic study from both femurs of 1 animal. In all of the animals the vitallium and stainless steel screws remained firmly fixed in place. The same was true

of the plates. None were loose. There was no evidence of any absorption of bone around any of the screws or under any of the plates (fig. 1). In 1 animal, however, both the stainless steel nail and the vitallium nail, which were driven into the trochanteric region of the femurs, were loose. This was due not to absorption of bone or corrosion of the nails but to the fact that the nails had been improperly inserted and passed through only a small amount of cancellous bone. The same error occurred in inserting the nails in both femurs of the animal. It should be stated that none of the nails, screws or plates were passivated before they were used.

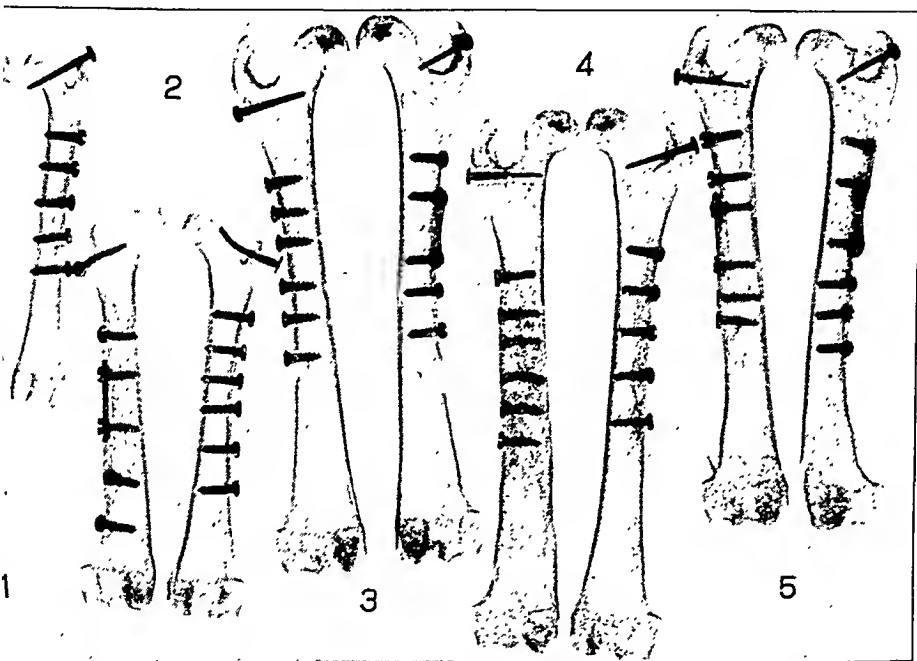


Fig. 1.—Paired femurs of 5 dogs thirteen months after the insertion of screws and nails. The screws and nails in the right femurs were of vitallium and those in the left femurs were of stainless steel. Specimens were removed from 3 for microscopic examination.

It was found that some of the plates and screws were partly covered by new bone and that a thin film, or capsule, of connective tissue covered the heads of the nails, screws or plates where they projected from, and were not covered by, the bone. At the time of the removal of the bones from the body none of the metal showed any evidence of corrosion. However, the bones were placed in a 10 per cent concentration of solution of formaldehyde U. S. P. and left for about nine months before they were cleaned and dried. During this interval in solution of formaldehyde

there appeared definite staining of tissues around some of the stainless steel nails, screws and plates. The staining was slight, but still it was definite. A similar staining of the tissues did not occur around the nails, screws or plates of vitallium. Also, it is to be noted that in the femurs which contained the stainless steel material there was a slightly greater amount of periosteal and endosteal new bone formation than there was around the vitallium.

Animal Experiment 2.—The second experiment consisted of cutting the two femurs of dogs obliquely and fixing them. In one femur plates and screws of stainless steel were so applied that the femur was rigidly fixed. In the opposite femur stainless steel wire was used, and the bone was fixed so that there was a small amount of play. The object of the experiment was to determine whether or not rigid internal fixation was advantageous for the union of bone. Unfortunately, the experiments have not been extensive enough to allow any conclusions to be drawn, and in several animals the plates bent or the femurs broke where they were drilled. As a result of these mishaps the wounds became infected, and the animals were killed. In those animals in which the internal fixation was mechanically strong enough to stand the strain of ordinary use, the bones united in the normal manner, regardless of whether they were rigidly or loosely fixed; and in none of these was there any evidence that the stainless steel wires, plates or screws interfered in any way with the normal union of the bone, and some of these bones united with a minimum of callus.

In microscopic sections of bone adjacent to the screws there was no evidence of any absorption or inflammatory reaction, and living bone was in direct contact with the metal and projected in between the threads. This was true of the bone around both the stainless steel and the vitallium screws.

Experiments to Determine Corrosibility.—In order to test the resistance of the stainless steel and of the vitallium to corrosion, screws, plates and nails were placed in physiologic solution of sodium chloride and left for six months or longer. It was noted that a variable amount of corrosion occurred in those jars which contained only the stainless steel and that the solution after a few days was stained brown. The reddish brown material, or rust, accumulated in the bottom of the jars or bottles. As the process continued the steel remained bright, but sharply localized pitting of some of the nails and plates was noted. This was particularly true of a group of old Smith-Petersen nails and old plates of stainless steel which were apparently not made of the 18-8 material.

However, if even the modern 18-8 stainless steel was left in the solution for several weeks or months, there occurred a variable amount of localized corrosion, with staining of the surrounding fluid. On the

and, if a piece of aluminum or a piece of vitallium was placed in the same vessel, the corrosion of the stainless steel was inhibited. In the case of the aluminum there was a considerable amount of corrosion, and the corroded material was set free in the fluid. Apparently, there must have been some corrosion of the vitallium, for otherwise it would not have been possible to inhibit the corrosion of the stainless steel by having vitallium present in the solution. There must be an electric current established between the inhibiting metal, that is, aluminum or vitallium, and the stainless steel in order to prevent the corrosion of the steel.

When pieces of copper were placed in the same solution with the stainless steel, they tended to accelerate the corrosion. The same was true of pieces of copper placed in salt solution with vanadium steel. Aluminum, on the other hand, tended to decrease the corrosion of vanadium steel but by no means prevented it, as it did in the case of the 18-8 stainless steel.

To test the effect of immersion in salt solution, pieces of 18-8 S-MO, or enduro, stainless steel, were placed in the salt solution and kept in an oven at 58 C. (136.4 F.) for two months in order to accelerate any changes due to corrosion or electrolysis. This experiment was controlled by keeping similar jars containing stainless steel, vanadium steel and vitallium under the same conditions. The vitallium and the 18-8 S-MO, or enduro, steel showed no evidence of corrosion over the period of two months at the elevated temperature, whereas the other steels showed corrosion. Apparently, the increased temperature accelerated the corrosive process. It is thus evident that vitallium is less subject to corrosion than is standard 18-8 stainless steel and is practically the same in this respect as is the enduro stainless steel.

Physical Properties of Vitallium and Stainless Steel.—Vitallium is an alloy which must be cast and cannot be machined or drawn out to form wire. Consequently, its use is limited to the type of prostheses which can be made by casting. Likewise, it is subject to the limitations of cast products; that is, the vitallium screw or plate may contain blow holes or air holes and is subject to shrinkage. Stainless steel, on the other hand, can be cold rolled, machined and drawn into wire, and its hardness and brittleness can be altered by tempering. It has also been noted by Dr. J. A. Carnes that the resistance to vibration of vitallium is relatively slight as compared with that of 18-8 stainless steel. The vitallium plate broke after being vibrated 47 times, while that of stainless steel broke after being vibrated 2,000 times. Likewise, the vitallium cracked when bent to an angle of 25 degrees, while the stainless steel cracked when bent to an angle of 180 degrees (Carnes¹⁶). A stainless steel plate was bent approximately 25 degrees by a force of 25 pounds (11.3 Kg.),

16. Carnes, J. A.: Personal communication to the author.

while a vitallium plate of approximately the same size and shape was bent to a similar angle by a force of 12 pounds (5.4 Kg.).

In an attempt to measure the difference in electric potential two 18-8 stainless steel plates or screws were placed in salt solution and a micro-ammeter was attached to each; the current produced was scarcely sufficient to move the needle of the ammeter. When enduro steel or vitallium was tested under the same conditions there was usually no perceptible movement of the needle, but sometimes a slight movement was seen. In other words, it is believed that the electric current between two pieces of stainless steel is not strong enough to be of any importance, but it is slightly more marked than is the current generated by two pieces of vitallium or by two pieces of enduro stainless steel under the same conditions.

COMMENT

My observations indicate that vitallium has a slight advantage over ordinary 18-8 stainless steel as regards corrosion, or electrolysis (the terms may be used interchangeably). However, it does not seem to have any such advantage over enduro, or 18-8 S-MO, stainless steel, which is now available at relatively small cost and can be obtained by all instrument makers. Stainless steel has a great advantage over vitallium in that it can be machined and drawn into wire, cold rolled and tempered to varying degrees of hardness. It is also stronger than vitallium, is less brittle and is more resistant to fatigue. Finally, vitallium is relatively expensive, and its output is controlled by one company, while stainless steel is relatively cheap and is readily available from many sources.

The question that arises is how important is the slight amount of corrosion which may occur in 18-8 stainless steel plates and screws which are left in the body over a period of years. It is my opinion that corrosion, or electrolysis, if one prefers to use that term, has relatively little to do with the success or the failure of the operation when a prosthesis is used for the internal fixation of bone.

Even when corrosive material was used I never had to remove a prosthesis because the metal caused infection, absorption or softening of the bone or interfered with the formation of callus. On one occasion I removed a Parham band from the tibia, and on another occasion I removed screws from a bone graft of the tibia. The Parham band had been in place eight years, and at the end of this time, when the patient had reached maturity, redness, edema and pain developed over the site of the band. It was removed with considerable difficulty, because it was corroded and almost completely covered by bone. The screws which I removed had been used to fix a bone graft on a tibia which had been badly infected. After union occurred one of the screws became painful. All of these screws, which were of vanadium steel, were found to be loose and were removed. I have on many occasions fixed bone grafts to long

with vanadium steel screws, and with the exception of those used in the case mentioned, I believe these screws are still in place. Vanadium steel screws were used because stainless steel screws of the Sherman self-tapping type were not available in this country until three or four years ago.

It has been my experience that if the vanadium steel screw is properly placed and is not too close to the skin it, or the plate which it may have been maintaining in position, can remain in place indefinitely. On the



Fig. 2.—Site of fracture of the hip over five years after nailing. In spite of the marked corrosion of the old type, stainless steel nail there are no symptoms.

other hand, if it is close to the skin it probably will have to be removed. The same is true of the ordinary soft iron, or stovepipe, wire which was used before stainless steel was available. I have not had to remove it on account of corrosion, or electrolysis.

When stainless steel wire, screws and nails became available I began to use them and have used them since. On no occasion have I had any trouble which could be attributed to the material of which the wire, nail or screw was composed. Venable and Stuck suggested that corrosion of

chromium-plated steel plates might cause chromium poisoning. Figure 2 shows a nail which was made of the wrong kind of stainless steel. After five years it is markedly corroded and has even been corroded in two, and yet the patient is in perfectly normal health, has maintained firm union and has an apparently normal hip. I believe that the chromium is not liberated in a poisonous form.

I have removed nails from hips only because they projected too far out from the bone and caused pain, because there was failure of union, because there were absorption and shortening of the neck of the femur before union occurred or because of necrosis of the head of the femur. I have not removed any stainless steel prosthesis on account of corrosion, nor do I know of any instance in which this has been necessary when 18-8 stainless steel was used. For the internal fixation of bone a prosthesis of vanadium steel or other corrosive metal may be used with confidence if a suitable prosthesis of stainless steel or vitallium is not available. If it is sterile and mechanically right, such a prosthesis will maintain fixation until union has occurred, and its removal will rarely be necessary unless it is too close to the skin.

As was noted in the incomplete review of the literature which is included in this paper, several observers have warned against placing two different metals close together in the tissues, because they then form a small battery and the electric current which they generate accelerates corrosion and may even affect the tissues. This is undoubtedly true of corrosive metals. Whether it is true of noncorrosive metals, such as the various stainless steels and vitallium, is doubtful.

CONCLUSIONS

Vitallium, 18-8 stainless steel and 18-8 S-MO, or enduro, stainless steel are inert in the tissues, and all are suitable for the internal fixation of bone.

The mechanical advantages of the stainless steel of the 18-8 type outweigh its slight tendency to corrosion, or electrolysis; and it is a more generally useful material for the internal fixation of bone than is vitallium.

The 18-8 S-MO, or enduro, stainless steel is even more suitable than is the ordinary 18-8 stainless steel.

The Fracture Committee of the American College of Surgeons should recommend the standardization of 18-8 S-MO, or enduro, stainless steel for the manufacture of prostheses for the internal fixation of bone and should require such prostheses to be properly labeled or stamped in order that surgeons may know what type of stainless steel they are using. The prostheses should be passivated by the manufacturer.

When and if a more suitable material is discovered, it should be adopted.

TRAUMATIC CHYLOTHORAX

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AND

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CINCINNATI

Traumatic chylothorax is a relatively rare condition. In a recent comprehensive review of the subject, Shackelford and Fisher¹ were able to collect only 43 authentic cases. They not only emphasized the rarity of traumatic chylothorax but also stressed the difficulty both of making an early diagnosis and of treating this condition. The reported mortality is approximately 50 per cent in spite of the various methods of therapy.

The causation of chylothorax has been summarized by McNab and Scarlett² as follows:

- I. Trauma
 - a. Closed trauma
 1. Without fracture of bone
 2. Accompanied by fracture of ribs, clavicle or vertebrae
 - b. Operative wounds
 1. Duct severed
 2. One or more terminals severed
 - c. Gunshot or stab wounds
- II. New growth or granuloma outside the duct:
carcinoma, lymphosarcoma, tuberculous glands
- III. Thrombosis of the left subclavian vein
- IV. New growth within the duct
- V. Perforating lymphangitis
- VI. Aneurysm of the duct
- VII. Cirrhosis of the liver
- VIII. Filariasis

The anatomy of the thoracic duct has been well described by numerous authors.³ Several facts are worthy of repetition, namely, that the

1. Shackelford, R. T., and Fisher, A. M.: Traumatic Chylothorax, *South. M. J.* **31**:766-775, 1938.

2. McNab, D. S., and Scarlett, E. P.: Traumatic Chylothorax Due to Intra-thoracic Rupture of Thoracic Duct, *Canad. M. A. J.* **27**:29-36, 1932.

3. Rouvière, H.: Anatomy of the Human Lymphatic System, translated by M. J. Tobias, Ann Arbor, Mich., Edwards Bros., Inc., 1938.

duct is normally present on the right side in the lower part of the thorax and that anomalies of displacement and doubling of the duct occur.

The physiologic significance of a ruptured thoracic duct is readily understood when one realizes that 60 per cent of ingested fat passes along the duct channel,⁴ that from 130 to 195 cc. of chyle is conducted each hour through the duct to the veins of the neck and that in cases of rupture frequently 2 liters or more of chyle collects daily in the chest. The protein content of the chyle varies from 1 to 6 Gm. per hundred cubic centimeters.⁵ Such a loss of fluid so rich in protein and fat leads readily to inanition and dehydration if not replaced by various forms of therapy.

In a recent case of chylothorax following an operative procedure, which is the first one of its type to be reported, we were able to make certain studies which have not hitherto been reported and to employ more extensively than ever before the therapy of returning the aspirated chyle intravenously to the patient.

REPORT OF A CASE

A 17 year old white girl entered the hospital Feb. 5, 1941 with a sarcoma on her right tenth rib. Her general health was good. In the region of the ninth and tenth ribs posteriorly there was a diffuse smooth swelling. A friction rub could be heard over the tumor, but no alteration in the lung tissue could be made out. Roentgenograms of the chest showed destruction of the right tenth rib extending from the rib's attachment with the vertebra nearly to the costochondral junction (A in fig.). Roentgenograms of the remainder of the skeletal system revealed no abnormalities. A general physical examination, including laboratory studies, revealed nothing of importance.

At operation all but a short segment of the anterior portion of the tenth rib was resected. The pleura beneath and the intercostal muscles above and below it were excised. The lesion was Ewing's tumor of the rib. It extended well into the thoracic cavity and over close to the body of the tenth vertebra. The large vessels were ligated with silk, but some general ooze in the bed of the wound was controlled with the Bovie unit. Just before closing the chest Dr. Mont Reid, the operator, noted some turbid fluid welling up in the bed of the wound and suspected that the thoracic duct had been resected with the growth. The duct could not be seen or ligated. Before the dressing was applied, all the air was aspirated from the chest. Complete expansion of the lungs was confirmed by a roentgenogram taken immediately after operation.

The first two postoperative days were relatively smooth. On the third day, after a severe coughing spell, the patient experienced a sharp pain in the right side of the chest. She became dyspneic but not cyanotic. Physical examination at the time revealed fluid in the right side of the chest; this was confirmed by

4. Bloor, W. R.: Fat Transport in the Animal Body, *Physiol. Rev.* 2:92-115, 1922.

5. Drinker, C. K., and Field, M. E.: Lymphatics, Lymph and Tissue Fluid, Baltimore, Williams & Wilkins Company, 1933.

roentgenogram. On the fifth postoperative day a thoracentesis was performed, and 900 cc. of turbid pink-tinged liquid was obtained. Both smear and culture of the fluid were negative for bacteria. The specific gravity was 1.019. Wright's stain revealed numerous red blood cells and a few white blood cells (90 per cent lymphocytes). With sudan III stain, many fat globules were seen, and a lipocrit determination⁶ revealed 0.36 cc. per hundred cubic centimeters of fluid. On the basis of these examinations we believed the fluid to be chyle.

During the course of the next twelve days 7,800 cc. of chyle was removed by five thoracenteses (*B* in fig.). After the first aspiration the fluid assumed the typical milklike appearance as the blood contamination decreased. Four intravenous administrations of chyle were given, totaling 3,000 cc. After the fifth thoracentesis on the fourteenth postoperative day there was no further accumulation of chyle.

After the fifth postoperative day the patient's temperature was never elevated above 99 F., except for a mild thermal reaction after an intravenous treatment. The patient was discharged on her twenty-fourth postoperative day. A roentgen examination of the chest then revealed no evidence of reaccumulation of chyle (*C* in fig.). At the time of her discharge from the hospital her nutrition and strength were good; the total loss in weight was only 10 pounds (4.5 Kg.). At the time of writing, she had been home for two months and in spite of high voltage roentgen therapy had regained 8 pounds (3.6 Kg.).

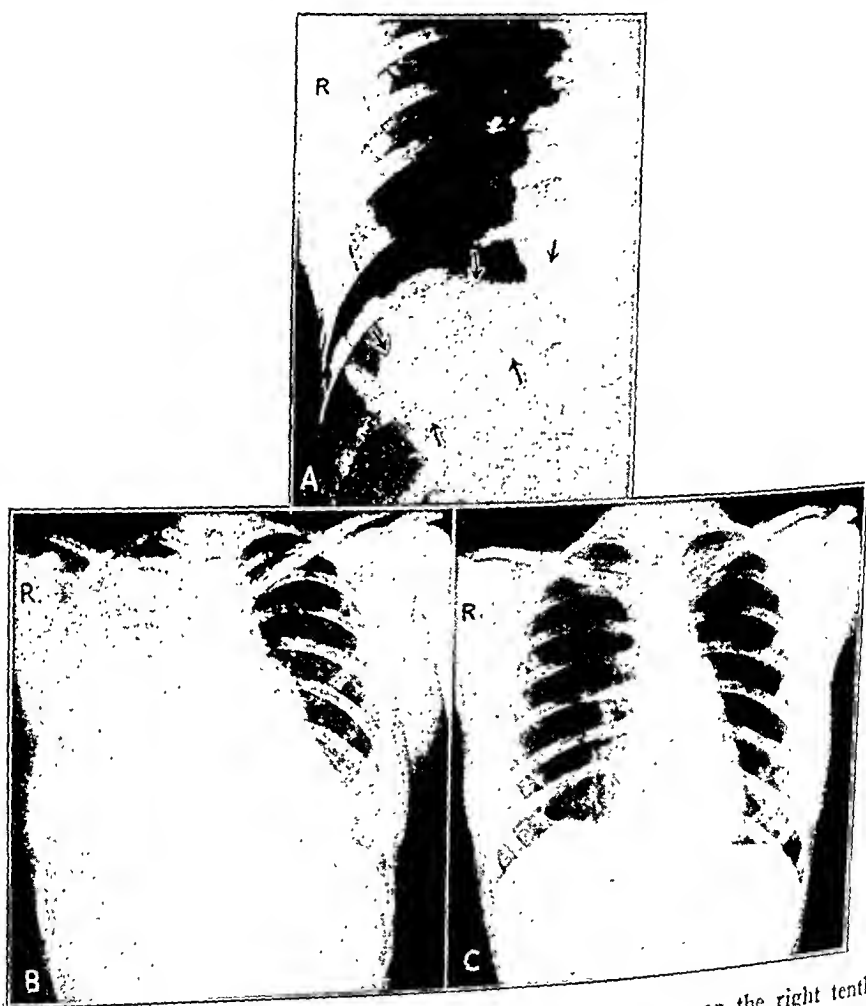
COMMENT

The chylous fluid removed in this case exhibited the following characteristics: It was a milklike fluid that formed three layers on standing, an upper "cream" layer, a middle "milk" layer and a lower sediment layer, consisting chiefly of the cellular elements. On standing for a long time a small coagulum formed. The specific gravity ranged from 1.016 to 1.025. The protein content varied from 3 to 6 Gm. per hundred cubic centimeters. These values were checked by both the falling drop and the Kjeldahl methods. The presence of fat was determined by three methods: (1) staining with sudan III, (2) shaking the chyle with ether and (3) the lipocrit method.⁶ By the latter method the fat content varied from 0.4 to 2.8 cc. per hundred cubic centimeters. The chyle was always alkaline in reaction and contained relatively few red blood cells and leukocytes, 90 per cent of the latter being lymphocytes. Repeated cultures of the aspirated chyle were sterile.

Numerous investigators⁵ have emphasized the decrease of lymphocytes circulating in the blood after ligation of the thoracic duct. In our case we noted a drop in the percentage of lymphocytes from 39 before operation to 17 three days after operation. This persisted without return to the preoperative level. We mention this point as a possible aid to diagnosis in cases in which injury of the thoracic duct is suspected.

6. Herrmann, L. G.; Ames, A., and Tapke, R. J.: Observations upon the Lipocrit Method, *J. Lab. & Clin. Med.* 19:411-421, 1934.

The treatment of chylothorax must satisfy several requirements, namely, prevention of the loss of chyle, maintenance of nutrition and prevention of infection in the chest. As traumatized thoracic ducts often close or heal spontaneously, and as operation is not often feasible because of the inaccessibility of the duct or because of the patient's condition, we feel that operation is not advisable, at least during the



A, roentgenogram taken before operation, revealing tumor on the right tenth rib. *B*, roentgenogram of the chest taken fourteen days after operation, revealing extensive chylothorax on the right side. *C*, roentgenogram of the chest taken on the day of discharge from the hospital, revealing no reaccumulation of chyle.

early stages. In our case we instituted conservative therapy, aspirating the chyle to prevent respiratory distress and giving the patient a diet low in fat to decrease the flow of chyle. To satisfy the nutritional requirements of the patient we felt that the intravenous administration of the chyle was the most physiologic. Oral and rectal administration of chyle have been reported, and two investigators have given chyle

intravenously in the past. Bauersfeld⁷ in 1937 gave his patient 1,200 cc. of chyle intravenously without a reaction. However, this therapy was instituted sixteen days after the original injury, and by this time the patient was quite weak and emaciated. Bauersfeld stated that after the administration of the chyle the patient promptly improved. The chyle ceased to reform in the chest, and the patient recovered. Oeken⁸ in 1908 attempted this procedure, but the patient did not recover. By early intravenous administration of the chyle in our case we prevented the weakness and wasting that result from the loss of this fluid.

TABLE 1.—*Examinations of the Blood of a Patient with Traumatic Chylothorax*

Date	Erythrocyte Count	Hemoglobin (Gm.)	White Blood Cell Count	Lymphocytes	Polymorpho-nucleurs	Monoocytes	Eosinophils	Basophils	Hematocrit (Volume per Cent)	Plasma Protein (Gm. per 100 Cc.)
2/ 6/41	4,250,000	12.2	5,600	39	55	3	2	1		
				(Before operation)						
2/ 9/41	3,830,000	6,200							
2/13/41	3,920,000	11.6	8,050	17	80	3	0	0		
2/14/41	4,530,000	12.7	10,150	45.0	6.15
2/16/41	5,140,000	14.9	13,400	18	77	0	3	2	48.9	6.13
2/19/41	4,670,000	13.4	6,550	47.2	7.33
5/12/41	4,150,000	11.4	4,400	25	67	5	2	1		

TABLE 2.—*Examinations of Chyle Obtained by Thoracenteses*

Date	Amount, Cc.	Specific Gravity	Protein, Gm. per 100 Cc.	Fat, Cc. per 100 Cc.	Culture
2/12/41	900	1.0250	6.00	0.4	Sterile
2/13/41	1,500	1.0172	3.38	1.2	Sterile
2/16/41	1,800	1.0252	6.11	1.2	Sterile
2/18/41	2,100	1.0160	2.97	2.8	Sterile
2/21/41	1,500	1.0165	3.14	2.0	Sterile

Hematocrit, lipocrit and plasma protein determinations were made at regular intervals.

In collecting the fluid from the thorax we used the closed technic. Sodium citrate was added to the collected chyle at the time of aspiration to prevent clotting. Cultures were made and the fluid placed in the ice box until a twenty-four hour negative culture had been obtained. Thoracentesis was done only as warranted by the clinical condition of the patient. Five aspirations were performed and a total of 7,800 cc. of chyle removed.

7. Bauersfeld, E. H.: Traumatic Chylothorax from Ruptured Thoracic Duct Treated by Intravenous Injection of Aspirated Chyle, J. A. M. A. **109**:16-18 (July 3) 1937.

8. Oeken: Ein Fall von Zerreißung des Ductus thoracicus infolge Brustquetschung, München. med. Wchnschr. **55**:1182-1183, 1908.

Four intravenous administrations of chyle were given, totaling 3,000 cc. On one occasion the patient experienced a slight chilly sensation, and her temperature rose to 100 F. Other than this, no reactions occurred. It was felt that this slight reaction could be attributed to a too rapid giving of the fluid. We felt no hesitancy in storing the chyle, and chyle as old as four days was given. Determinations of blood fat were made before and after the administration of the chyle. The patient's fasting blood fat level fell slowly over a period of a week from the initial figure of 0.42 to 0.32 cc. per hundred cubic centimeters. We feel that the gradual lowering of the fat level must have been due to the fact that the diet was low in fat and to our failure to reinject all the aspirated chyle. As would be expected, a rise in the blood fat followed each administration of chyle. Twenty-eight days after operation, after the patient had been receiving a regular diet, and no evidence of any further accumulation of chyle in the chest

TABLE 3.—*Observations on Intravenous Administration of Chyle*

Date	Amount, Cc.	Reaction	Blood Fat, Cc. per 100 Cc.		
			Fasting	At End of Injection	Two Hours After Injection
2/17/41	700	None	0.42		0.33
2/19/41	600	Chilly sensation	0.35	0.51	
2/20/41	700	None	0.36	0.55	
2/22/41	1,000	None	0.32	0.61	
3/17/41	0.50		

had been noted, the fasting fat level was 0.48 cc. per hundred cubic centimeters. The importance of the third requirement in the treatment of chylothorax, namely, the prevention of infection in the chest, is apparent. Obviously, infected chyle cannot be given intravenously.

SUMMARY

A case of traumatic postoperative chylothorax is presented together with certain observations on the chemistry of the chyle and the patient's blood.

The rarity of this condition is emphasized by the fact that we were able to find only 43 previously reported cases of traumatic chylothorax, in none of which was the condition postoperative.

The rapid emaciation can be prevented by intravenous administration of the aspirated chyle.

Open external drainage of the chyle should be avoided, unless empyema supervenes. The chyle should be aspirated only to relieve respiratory distress, for its accumulation under pressure probably helps to close the fistula.

DIFFERENTIATION OF SURGICAL JAUNDICE FROM SEVERE DAMAGE OF LIVER (SUBACUTE YELLOW ATROPHY) CLINICALLY SIMULATING IT

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With the discovery of vitamin K and the development of methods for measuring plasma prothrombin levels, operation on the jaundiced patient lost much of its terror. By simple preoperative and postoperative procedures, abnormal bleeding in most cases of obstruction of the common duct, whether by stone, tumor or stricture, can now be anticipated and prevented. The liver in these cases is usually normal or so little impaired that the prothrombin level is rapidly brought to normal when the body is given an adequate amount of vitamin K and of bile or bile salts. It has been well established that if the prothrombin level remains normal, unusual bleeding in uncomplicated obstruction of the common duct does not occur.

The diagnosis of common duct stone may often be fairly clear, particularly when gallbladder colic, chills, fever and jaundice are present. The preoperative diagnosis of carcinoma of the head of the pancreas or bile ducts may be less positive, since progressive silent jaundice and acholic stools are often the only basis for such a diagnosis. Cholecystography may be of a little aid in these cases.

Laparotomy in the jaundiced patient is still in a great many cases an exploratory procedure. Silent jaundice is usually considered to represent an obstruction of the bile passages due to malignant growth until proved otherwise, and an exploratory operation is done with the faint hope that the obstructing factor is a stone or multiple stones. In cases in which there has been previous operation in the region of the bile passages, stricture may be suspected. When carcinoma of the head of the pancreas or bile ducts is found, either the abdomen is closed without further operation, or one of several procedures to relieve the jaundice is carried out. However, with subacute yellow atrophy or any other severe pathologic condition of the liver, often unsuspected before operation, the patient may fail to survive even an exploratory laparotomy.

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THE LIVER AS A SOURCE OF PROTHROMBIN

Warner, Brinkhous and Smith first suggested that the measurement of plasma prothrombin may be used as an estimate of liver function.^{1b} They demonstrated that dogs having chloroform or phosphorus intoxication show rapid development of prothrombin deficiency, the degree corresponding to the degree of hepatic damage.¹ The return to higher levels corresponds in time and degree to the regeneration of liver tissue. Warner² found that rats from which the major portion of the liver has been removed show a rapid drop in plasma prothrombin.

A number of investigators³ have observed that patients with cirrhosis of the liver have lowered prothrombin levels and that the response to vitamin K therapy in such cases is usually poor. Wilson⁴ in a study of patients with and without impairment of the liver compared the hippuric acid synthesis and prothrombin level, determined by the two stage method, as tests of liver function. Both, he found, were sensitive tests of hepatic impairment. It is fairly well established, then, that the liver is the site of prothrombin formation and that damage of the liver is accompanied by a lowering of that substance in the blood plasma.

The prothrombin levels in 62 cases of jaundice have been studied in this laboratory in the past two years by the two stage method of Warner, Brinkhous and Smith.^{1a} A positive diagnosis of common duct stone was made in 13 cases and a provisional diagnosis in 4 other cases. Carcinoma of the head of the pancreas was diagnosed and the diagnosis confirmed in 16 cases, carcinoma of the common bile duct in 2 cases, and of the papilla of Vater in 1 case. There were 3 cases in which a clinical diagnosis of catarrhal jaundice was made, and 21 cases in which cirrhosis of the liver was diagnosed on the basis of the history and

1. (a) Warner, E. D.; Brinkhous, K. M., and Smith, H. P.: A Quantitative Study of Blood Clotting: Prothrombin Fluctuations Under Experimental Conditions, *Am. J. Physiol.* **114**:667-675, 1936. (b) Smith, H. P.; Warner, E. D., and Brinkhous, K. M.: Prothrombin Deficiency and the Bleeding Tendency in Liver Injury (Chloroform Intoxication), *J. Exper. Med.* **66**:801-811, 1937.

2. Warner, E. D.: Plasma Prothrombin: Effect of Partial Hepatectomy, *J. Exper. Med.* **68**:831-835, 1938.

3. (a) Scanlan, G. H.; Brinkhous, K. M.; Warner, E. D.; Smith, H. P., and Flynn, J. E.: Plasma Prothrombin and the Bleeding Tendency, *J. A. M. A.* **112**:1898-1901 (May 13) 1939. (b) Bollman, J. L.; Butt, H. R., and Snell, A. M.: The Influence of the Liver on the Utilization of Vitamin K, *ibid.* **115**:1687-1691 (Sept. 28) 1940. (c) Olwin, J. H.: The Intravenous Use of Vitamin K, *ibid.* **117**:432-435 (Aug. 9) 1941.

4. Wilson, S. J.: Quantitative Prothrombin and Hippuric Acid Determinations as Sensitive Reflectors of Liver Damage in Human Subjects, *J. Lab. & Clin. Med.* **25**:1139-1145, 1940.

physical findings of a large liver with ascites, edema of the lower extremities and dilated superficial abdominal veins. In these the jaundice was of a mild degree. A diagnosis of acute alcoholic hepatitis was made in 2 cases.

Patients with obstruction of the common duct whether from stone, tumor, stricture or other obstruction may vary widely in their prothrombin levels, depending on the duration of the jaundice and on the general nutrition and diet. Nearly all of these patients, except those in the later stages, showed prompt response to vitamin K therapy, the prothrombin levels coming to near normal in one to four days as a rule, even in instances in which the levels have been extremely low^{3c}; in some cases a little longer period is required. Without exception all of our patients showed a material rise.

Patients with hepatic cirrhosis show varying levels of plasma prothrombin; in our series the values of original determinations ran between 30 and 90 per cent. If the damage of the liver is not too severe or has not been present too long, a small percentage of these patients with prothrombin deficiency will show some response to vitamin K therapy. However, in most of them the prothrombin level is little affected, even when large doses of the vitamin and of bile salts are given over long periods. (It is interesting that even though the prothrombin is raised but little, many of these patients are remarkably improved clinically without rest in bed and without other treatment.) In the patients with acute alcoholic hepatitis the prothrombin was originally 57 and 77.6 per cent. After treatment the values for these patients came to 88.8 and 106 per cent, respectively.

TEST OF LIVER FUNCTION

These results indicate that rather than the original prothrombin level, the response of the liver to vitamin K as reflected in the prothrombin rise is the important point in the measure of liver function. In order to eliminate the factor of absorption of vitamin K from the gastrointestinal tract, which in certain cases may be greatly impaired, it has been the routine practice in this laboratory since December 1939 to give the vitamin intravenously. The synthetic 2-methyl-1,4-naphthoquinone (menadione)⁵ is effective in small doses; in some cases as little as 0.1 mg. is enough to bring the prothrombin level to normal.^{3c} It has been the practice to make an original prothrombin determination and, if this is low, to administer 2 mg. of the material intravenously and recheck the prothrombin after twenty hours. If it is still below 100 per cent, a second dose is given, and the prothrombin level taken again forty-four hours after the first dose. Most patients with good liver function will

5. The yellow crystals were supplied to us by E. R. Squibb & Sons.

show a normal or nearly normal level at this point. Patients who fail to respond normally are then given oral preparations⁶ with occasional supplementary intravenous doses of the material, depending on the type of patient being treated. Prothrombin levels are taken at frequent intervals, and, as can be seen in tables 1 and 2, daily improvement in liver function can be accurately followed.

Three patients with severe jaundice failed to show the usual response.

REPORT OF CASES

CASE 1.—A. F., a 65 year old obese white woman, entered the Presbyterian Hospital on Nov. 14, 1939 with a history of slowly deepening jaundice during

TABLE 1.—*Representative Responses in Cases of Obstruction of the Common Bile Duct*

Diagnosis	Prothrombin Level (Per Cent of Normal)							
	1st Day	2d Day	3d Day	4th Day	5th Day	6th Day	7th Day	8th Day
Carcinoma of head of pancreas..	49.5	65.2	84.9
Carcinoma of head of pancreas..	13.9	22.4	43.3	81.4	89.1
Carcinoma of head of pancreas..	83.5	106.0
Carcinoma of head of pancreas..	88.3	115.0
Carcinoma of head of pancreas..	40.9	67.4	102.2
Carcinoma of head of pancreas..	39.0	49.1	70.4	82.3
Carcinoma of head of pancreas..	45.4	80.4	91.0
Carcinoma of head of pancreas..	85.6	101.0
Carcinoma of head of pancreas..	83.4	90.4
Carcinoma of head of pancreas..	67.2	84.0	91.2
Carcinoma of head of pancreas..	82.6	108.3
Common duct stone.....	83.2	103.2
Common duct stone.....	89.7	105.0
Common duct stone.....	88.4	98.5
Common duct stone.....	77.4	84.7	108.3
Common duct stone.....	79.6	85.0	94.0
Carcinoma of common duct.....	18.4	50.2	69.7	73.1
Catarrhal jaundice.....	39.7	73.8
Catarrhal jaundice.....	57.6	72.3	84.5

the previous four weeks. She had had a great deal of itching during this time and in the two weeks prior to admission had felt marked loss of strength. During the last week before admission she had noticed a dull soreness in the right upper quadrant of the abdomen. She had had no acute pains, chills or fever. Her appetite had always been good but had failed since the onset of the jaundice. There had been a loss of 10 pounds (4.5 Kg.) during this time. She stated her stools were white to clay colored in the early weeks of the jaundice but in the week before admission were normal in color. Her physician had been giving her "occasional injections" for high blood pressure. An appendectomy had been done in 1909 and a nasal operation in 1914. Her father had died at 101; her mother, at 56 of an unknown cause. Two sisters had died of tuberculosis.

The patient weighed 152 pounds (68.9 Kg.). Her temperature at its highest was 99 F., her pulse rate varied between 60 and 90, and her blood pressure

6. The oral preparation used was menadione (2-methyl-1, 4-naphthoquinone) furnished by E. R. Squibb & Sons, Eli Lilly & Co., Parke, Davis & Co., and Abbott Laboratories.

measured 174 systolic and 64 diastolic. The skin and scleras were jaundiced. Her liver was not palpable, but slight tenderness could be felt below the right costal margin. Her hemoglobin measured 80 per cent of normal; the red blood cell count was 4,100,000, and the white blood cell count was 15,000. The icterus index was 165; the direct van den Bergh test gave an immediate positive reaction. One stool obtained was light brown and showed a 1 plus benzidine reaction. The urine contained albumin (3 plus), bile (4 plus) and an occasional white blood cell. Bleeding time as measured by the Duke method was three minutes; the coagulation time was two and a half minutes.

A preoperative diagnosis of obstructive jaundice, probably from the carcinoma of the head of the pancreas, was made.

The prothrombin level as measured by the two stage method the day after admission was 26.8 per cent. The patient stated she had been receiving vitamin K before she came to the hospital. Following the determination of prothrombin, she was given 1 mg. of menadione (2-methyl-1, 4-naphthoquinone) in oil and 5 grains (0.32 Gm.) of bile salts orally three times daily. The following day the prothrombin level was 26.6 per cent. Medication was increased to 2 mg. of menadione and 5 grains (0.32 Gm.) of bile salts three times daily. The following morning the prothrombin level was 24 per cent. The patient was operated on on the same day. The surgeon observed the liver to be lying well up under the right costal margin; the head of the pancreas seemed normal, and a diagnosis of probable carcinoma of the common bile duct was made. A cholecystogastrostomy was done. Bleeding was not excessive during the operation. The patient was returned to her room apparently in good condition with a pulse rate of 72 and blood pressure of 119 systolic and 50 diastolic. The dressings two hours later were saturated with bright red blood. The postoperative course was steadily downhill, and the patient died eleven hours after the operation.

Postmortem examination revealed the abdominal cavity filled with dark blood. The liver was estimated at one half to two thirds of its normal weight. (Permission to remove the organs was not obtained.) The microscopic picture was that of subacute yellow atrophy with the normal structure of the liver entirely absent (fig. 1). In a few areas there were remnants of lobules, but in most places there were only small groups of hepatic cords. The biliary tract was not obstructed.

CASE 2.—A. C., a 56 year old white woman, was admitted to the Presbyterian Hospital on Sept. 7, 1940 with a history of slowly deepening jaundice for four weeks, itching of the skin, feeling of fullness in the epigastrium, belching, bloating and passage of flatus, loss of appetite and loss of 12 pounds (5.4 Kg.) in weight over a period of two months. It was her first attack of jaundice. She had never had gallbladder colic, chills or fever. Her stools had become light tan. She had had the usual diseases of childhood. Tonsillectomy had been done two years before the present illness. She had one son living and well; there had been no other pregnancies. Her mother died at 78 years of heart trouble and her father at 73 of kidney disease.

Physical examination revealed a moderately well developed, poorly nourished white woman of 56, weighing 116 $\frac{3}{4}$ pounds (53 Kg.). The skin and scleras were deeply jaundiced. Her pulse rate ranged from 65 to 90; her temperature was normal most of the time, occasionally reaching as high as 100.6 F., and her blood pressure measured 116 systolic and 78 diastolic. The liver was not palpable; and no abdominal masses were made out. The hemoglobin measured 65 per cent of normal; red blood cells numbered 3,330,000 and white blood cells 4,300 per cubic

millimeter. The urine showed 10 white blood cells per cubic millimeter of uncentrifuged specimen and was darkly stained with bile. Urobilinogen was present. Stools were for the most part clay colored; occasionally a tan-colored specimen was obtained. The benzidine reaction was positive, varying between 2 and 4 plus; some of the specimens showed neutral fats and numerous fatty acid crystals. The mercury bichloride test was negative for bile. No amebas or cysts were found on direct examination of the stools or on culture. Fluoroscopy revealed a normal outline of the stomach and duodenum. The blood Wassermann reaction was negative. The icterus index at the time of the patient's admission was 182; the direct van den Bergh test showed an immediate positive reaction. The blood cholesterol measured 213 mg., the esters 53 mg. and the total nonprotein nitrogen 26 mg. per hundred cubic centimeters. Albumin in the blood amounted to 2.79 and

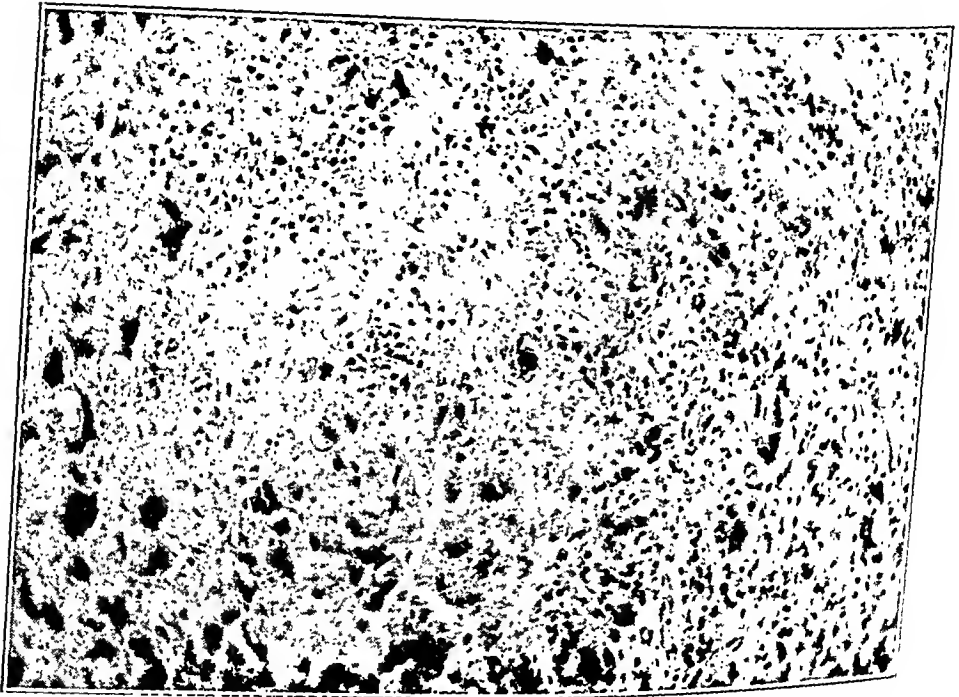


Fig. 1.—Photomicrograph of the liver of the patient in case 1, showing subacute yellow atrophy with the normal structure of the liver entirely absent.

globulin to 4.44 mg. Blood amylase was 157 units (normal, 200 units). The icterus index seventeen days after the original estimation was 211. Forty per cent of the gallbladder dye given intravenously was retained in the blood stream at the end of thirty minutes and 20 per cent at the end of sixty minutes. There was no evidence of gallbladder filling or of stone on the roentgen flat plate of the abdomen. The hippuric acid test for liver function showed excretion of 0.72 Gm., 24 per cent of normal. The prothrombin level four days after admission was 13.6 per cent.

The patient was given liver concentrate, vitamin C, the vitamin B complex and iron by mouth. She received also 100 mg. of nicotinic acid amide intravenously early every day. After the original determination of prothrombin the patient

7. The nicotinic acid amide was supplied by the Abbott Laboratories.

given 2 mg. of menadione intravenously. This was repeated the following day. From this point she was given 1 mg. of crystalline menadione and 5 grains (0.32 Gm.) of a preparation of iron and bile salts⁸ three times daily by mouth and frequent 2 mg. doses of the former intravenously.

Her prothrombin level went to 21.4 per cent the day after the original determination and climbed slowly until after six days of therapy it had reached 47.3 per cent. The patient had improved subjectively up to this time, but from this point she declined rapidly. Her prothrombin dropped slowly and steadily, even with large amounts of vitamin K and bile salts, and twenty days after the original determination it was 31.9 per cent (table 2). The patient's clinical picture was that of obstructive jaundice on the basis of a carcinoma of the head of the pancreas, common bile duct or papilla of Vater, the persistent blood in the stools strongly indicating the last named. On the evidence of the low prothrombin level and the poor response to vitamin K a diagnosis of a pathologic condition primary in the liver, possibly subacute yellow atrophy, was made, and the patient was not

TABLE 2.—*Prothrombin Fluctuations*

Case 1		Case 2		Case 3	
Date	Prothrombin (Per Cent of Normal)	Date	Prothrombin (Per Cent of Normal)	Date	Prothrombin (Per Cent of Normal)
November 15...	26.8	September 11...	13.6	June 11.....	36.7
16...	26.6	12...	21.5	12.....	36.8
17...	24.0	13...	27.8	13.....	36.4
		16...	33.0	14.....	35.4
		17...	42.0	17.....	43.7
		18...	45.9	18.....	50.7
		19...	47.3	19.....	51.9
		20...	45.6	20.....	60.4
		23...	40.6	21.....	64.0
		24...	34.6	24.....	74.8
		25...	33.7	25.....	82.2
		26...	32.7	26.....	65.0
		27...	34.5	27.....	90.5
		30...	35.2	28.....	96.5
		October 1...	31.9	July 1.....	96.2
				5.....	100.2

subjected to exploratory operation. Eighteen days after admission a mass about 6 by 6 cm. was palpable in the epigastrium 2 fingerbreadths below the ensiform cartilage. The liver was never felt at the right costal margin. In the last days of the patient's life subcutaneous hemorrhages appeared over most of her body. Her condition grew steadily worse, and she died twenty-five days after admission.

Postmortem examination revealed subacute yellow atrophy of the liver with recent pancreatitis and fat necrosis of the peripancreatic adipose tissue. The bile ducts were unobstructed. The liver weighed 945 Gm. On the surface of the right lobe there were coarse depressions, 3 to 4 mm. in depth, involving all of the superior surface and about 50 per cent of the lower surface (fig. 2). Sections made through this lobe revealed disseminated reddish brown regions where the hepatic lobules were inconspicuous (fig. 3). The surface of the left lobe was fairly smooth, there being only slight depressions where the lobules had disappeared. In the surface appearing when this lobe was cut, most of the lobules were still present. Microscopic sections showed a retention of about 75 per cent of the lobules in this lobe, but in the right lobe most of the hepatic cords had disappeared, and the stroma had collapsed (fig. 4).

8. The preparation was bilron, furnished by Eli Lilly & Co

The pancreas showed disseminated regions of necrosis with infiltration of polymorphonuclear leukocytes, plasma cells and macrophages in the interstitial tissue. Between the regions of necrosis the acinous structure was fairly well maintained.

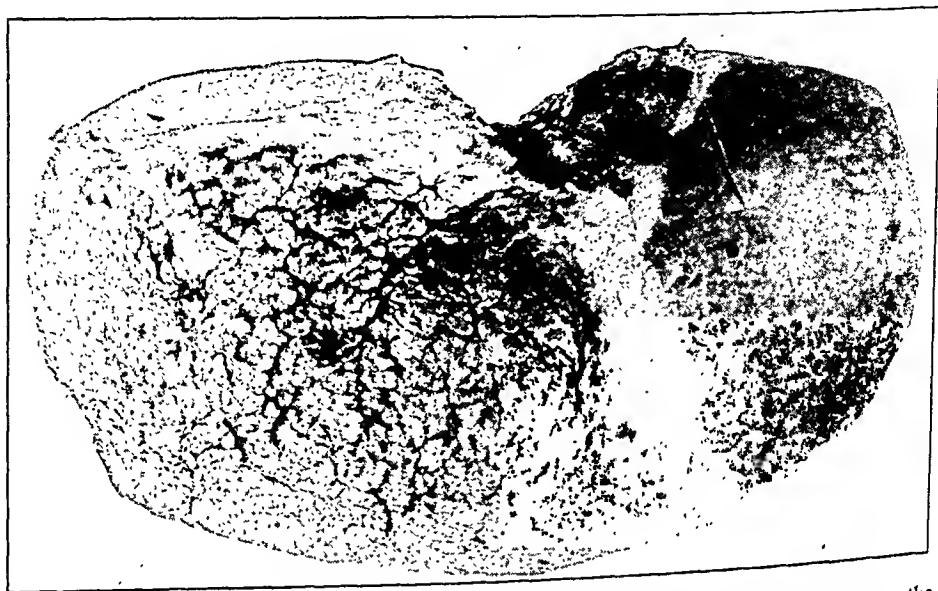


Fig. 2.—The liver of the patient in case 2. Note the coarse depressions on the surface of the right lobe and the much shallower ones on the left.

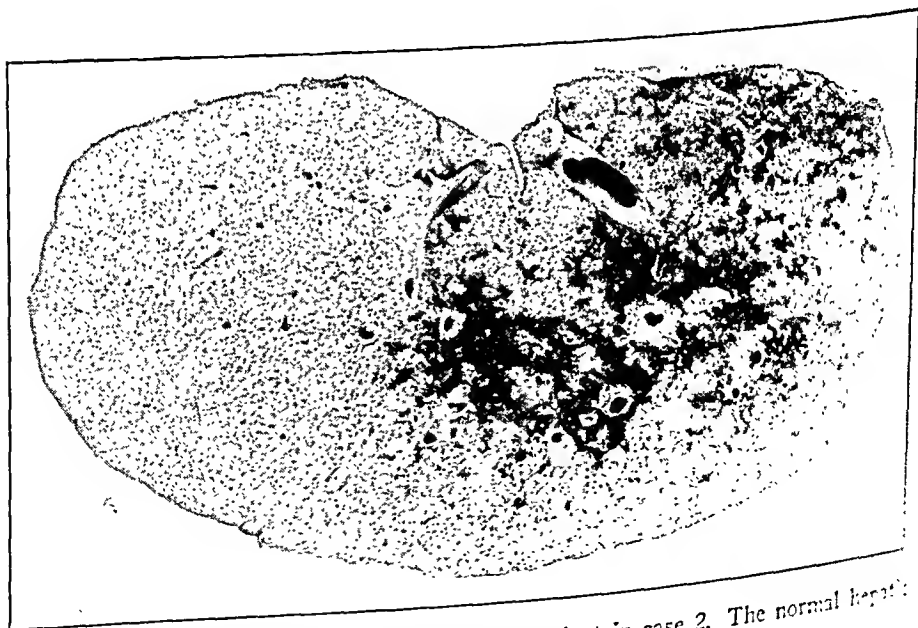


Fig. 3.—Section through the liver of the patient in case 2. The normal hepatic lobules are inconspicuous.

The relatively normal hepatic structure remaining in the left lobe may have accounted for the initial rise in prothrombin from 21.4 to 47.3 per cent. In case 1 there were no unchanged regions in the liver, and in only a few instances...

there remnants of lobules. In the three days on which the prothrombin level was taken in case 1, there was no response to vitamin K therapy.

CASE 3.—J. C., a 31 year old white woman, was admitted to the Presbyterian Hospital June 10, 1940, complaining of anorexia, nausea, weakness and dull pain in the epigastrium for one week. Four days before admission a slowly deepening jaundice was first noticed. At the time this was first apparent, she noticed swelling of her hands and wrists; this persisted for three days. She had been perfectly well until the onset of symptoms and had had no similar attack in the past. There had been no gallbladder colic, chills or fever. No history of her having taken drugs could be elicited. She stated her stools had been light in color during the two days prior to admission. Her mother died of diabetes; her father, of

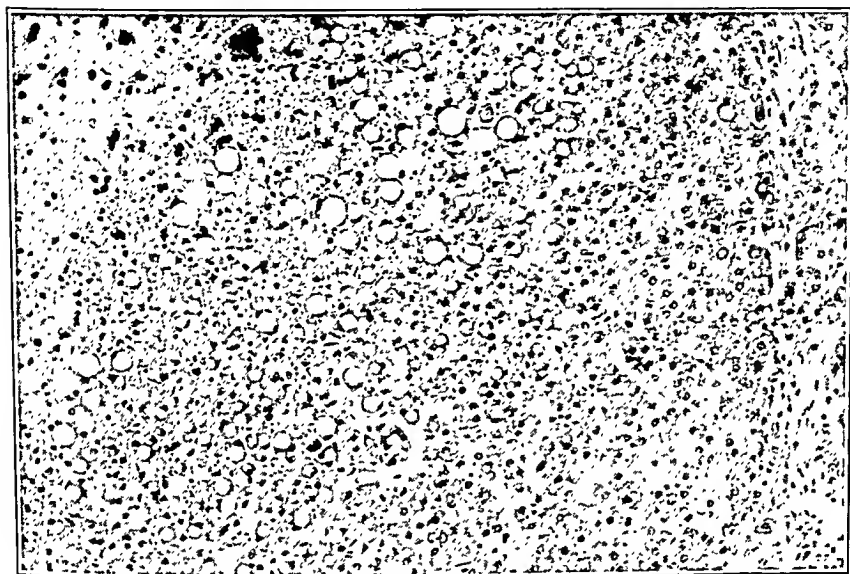


Fig. 4.—Microscopic picture from the right lobe of the liver of the patient in case 2. Most of the hepatic lobules have disappeared, and the stroma has collapsed. Note the deposits of fat.

"Bright's disease." She had had an appendectomy at the age of 12, a thyroidectomy at 21 and a tonsillectomy at 25.

Physical examination revealed a well developed and well nourished white woman deeply jaundiced. Neither her liver nor her gallbladder were palpable. Her blood pressure measured 125 systolic and 70 diastolic. Scars of her appendectomy and thyroidectomy were present. Physical examination disclosed nothing else of significance. The hemoglobin measured 83 per cent, the red blood cell count was 5,100,000 and the white blood cell count 6,100. Her urine contained bile (3 plus), no urobilinogen and no leucine or tyrosine crystals. An Ewald test meal showed 12 points of free acid and 16 points of total acids. The stools were gray with a questionable positive test for bile, were free of occult blood and contained a moderate amount of fat. No amebas were found on direct smear or culture. The icterus index at the time of the patient's admission was 107. A cholecystogram

revealed a nonfilling gallbladder. The rose bengal test for liver function showed complete retention of the dye at ten and eighteen minutes. Her excretion of hippuric acid expressed as benzoic acid was 0.268 Gm., 8.9 per cent of normal. The prothrombin level on the day following the patient's admission to the hospital was 36.7 per cent.

A 2 mg. dose of menadione was given intravenously on the second and third days after admission and from this point she received 0.6 mg. of the same material and 5 grains (0.32 Gm.) of an iron-bile salt preparation⁸ by mouth three times daily during the remainder of her stay at the hospital. She also received from this point 5 mg. of the vitamin B complex three times daily by mouth and 100 mg. of nicotinic acid intramuscularly. Her subsequent prothrombin levels are recorded in table 2. During the first four days she showed little change. Beginning the fifth day there was a slow steady rise in the prothrombin level until on the twenty-fifth day after her admission it was 100.2 per cent.

Her symptoms increased in severity after hospitalization, the nausea going into rather violent attacks of vomiting. About five days after admission her clinical condition began to improve, and this improvement continued until she was discharged June 29, feeling quite well. A rose bengal test for liver function on June 26 showed a 91 per cent retention of the dye at ten minutes and 71 per cent at eighteen minutes. On July 5 these readings were 76.6 and 58.2 per cent. The hippuric acid synthesis and excretion on June 25 was 0.571 Gm. (19.1 per cent) and on July 5 was 1.035 Gm. (33 per cent of normal). These tests did not give normal results as soon as did tests for the prothrombin level.

COMMENT

The patients in cases 1 and 2 and the patient in case 3 for the first five days of her hospital stay showed similarity in their prothrombin levels and in their response to vitamin K therapy. An exploratory operation was performed on the patient in case 1 for a probable carcinoma of the head of the pancreas. The patient in case 2 would ordinarily have been subjected to such an operation, but because of the similarity of prothrombin response in the 2 patients, surgical intervention was not carried out. In both cases postmortem examination revealed subacute yellow atrophy of the liver. The patient in case 2 would probably have succumbed to postoperative hemorrhage had she been subjected to operation.

The diagnosis in case 3 is questionable. Ordinarily, the patient's disease would have been considered catarrhal jaundice. Three cases of transitory silent jaundice in middle-aged patients have been studied. In the first there was no depression of the prothrombin. In the second the initial level was 57.6 per cent, and twenty-four hours after the patient received 1 mg. of menadione intravenously it came to 84 per cent. The other case showed a rise of from 39.7 to 73.8 per cent in three days. A diagnosis of catarrhal jaundice was made in each case. As mentioned before, in this study patients with obstructive jaundice from blockage of the common bile duct by tumor, stricture or stone have responded without exception to vitamin K therapy, most of them within twenty-

four hours after medication was started. Many patients with subacute yellow atrophy or similar severe damage of the liver do not recover, but some, like the patient in case 3, do. This patient, depending on her clinical course, might not have been subjected to operation, even without the prothrombin study, but patients falling in the group with those of cases 1 and 2 would have been operated on and possibly would have died immediately after operation.

Three cases are hardly enough on which to base definite conclusions, especially when autopsies were made in only 2. But the similarity of

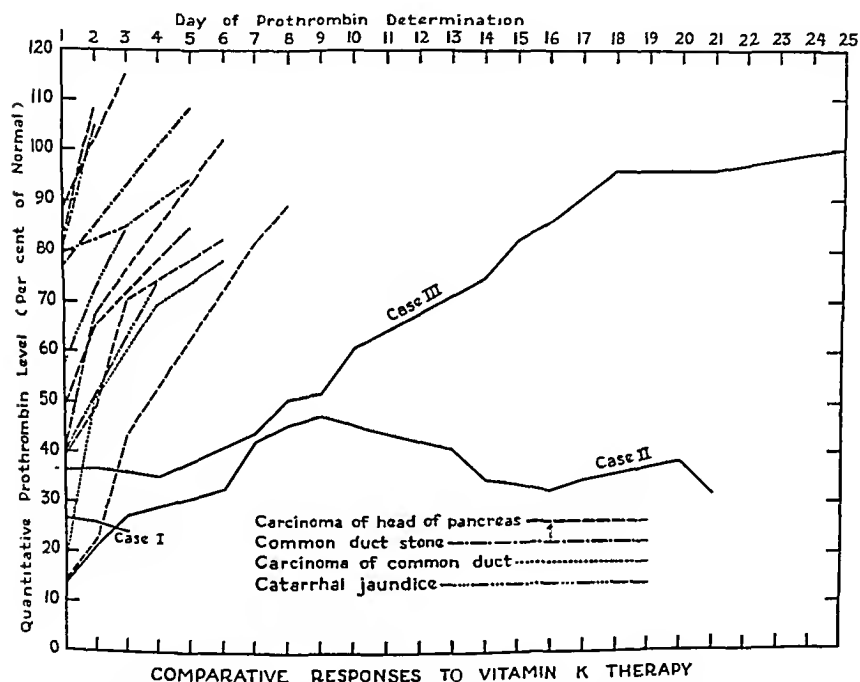


Fig. 5.—Comparative responses to vitamin K therapy in cases of obstruction of the common bile duct and cases of severe damage of the liver.

the prothrombin studies in the 3, combined with the severe damage of the liver in the 2 instances in which autopsies were made, definitely influences the procedure in cases of silent jaundice. Any patients who do not show a good and fairly prompt plasma prothrombin response to vitamin K therapy are not subjected to operation until the proper response occurs. Some of these patients will never show this response and will go on to death. However, they will have been spared the unnecessary expense and distress of a major surgical procedure. Others under medical management may recover. If they are subjected to oper-

ation, the severe damage to the liver may result in death from shock, postoperative hemorrhage or both.

It may be that with careful consideration of the history and physical findings and a study of the patient's response to vitamin K therapy, the two stage prothrombin determination will make possible a preoperative or premortal diagnosis in the majority of cases of subacute yellow atrophy of the liver.

SUMMARY

The two stage prothrombin determination as a measure of a patient's response to vitamin K therapy is a delicate test for liver function.

It offers promise of being a means of accurately distinguishing before operation between obstruction of the common duct from tumor or silent stone and severe damage of the liver, such as subacute yellow atrophy, which may clinically simulate obstruction of the common duct. Thus unnecessary surgical intervention and possible fatal postoperative hemorrhage may be avoided. Some of these patients with severe damage of the liver may recover.

The procedure described may be a means of making an accurate preoperative or premortal diagnosis of subacute yellow atrophy of the liver.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1940

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE
AMERICAN ACADEMY OF ORTHOPAEDIC SURGEONS

(Continued from page 540)

VII. INFANTILE PARALYSIS

General Considerations.—Members of the medical profession and laymen as well are becoming more interested in poliomyelitis owing to the interest of many lay organizations and to the activities of the National Foundation for Infantile Paralysis, such as grants in aid of research work, publications, special training of nurses and physical therapists and establishment of research fellowships for physicians.

During 1940 confirmation of the transmission of poliomyelitis to animals other than man and the monkey has been reported, and evidence demonstrating the alimentary tract as a pathway of entrance of the virus and spread of the disease has been adduced. Discussion of the use of hot moist applications during the acute stage of the disease has been reopened. There is an increasing trend of thought away from absolute, continuous, rigid immobilization of joints. Indirect laboratory evidence that a disease caused by a neurotropic virus can be successfully treated by serum is derived by Zichis and Shaughnessy²⁰⁸ from their work on equine encephalomyelitis. No further evidence has been reported to confirm the value of convalescent serum as a specific therapeutic agent.

Causation.—Aycock²⁰⁹ states that there is epidemiologic evidence that the virus of poliomyelitis is widespread but that the occurrence of the paralytic disease in those exposed to the virus is limited and selective. Some of the selectivities indicate that the determining factor between clinical and subclinical poliomyelitis resides in the host. A familial tendency suggests that this factor is inherent; seasonal and geographic selectivities indicate a physiologic rather than an anatomic character; association with a certain constitutional type points to an endocrine dysfunction; and the suspected selectivity seen in the occurrence of poliomyelitis during pregnancy, in view of the implication of the nasal mucosa as the portal of entry of the virus, suggests that estrogenic substances are concerned. Two series of experiments are described. In the first series the injection of estrogenic substance into castrated immature female monkeys enhanced their resistance to the intranasal instillation of the virus. In the second series there was studied a small number of

208. Zichis, J., and Shaughnessy, H. J.: Experimental Western Equine Encephalomyelitis: Successful Treatment with Hyperimmune Rabbit Serum, *J. A. M. A.* **115**:1071-1078 (Sept. 28) 1940.

209. Aycock, W. L.: Subclinical Endocrinology as a Factor in Autarceologic Susceptibility to Poliomyelitis, *Endocrinology* **27**:49-57 (July) 1940.

comparative estrogen assays of the urine of patients with poliomyelitis and that of normal persons. The results indicate a higher average excretion of estrogenic substance in the group of patients with poliomyelitis. These observations suggest that an autarcetic susceptibility to poliomyelitis may lie in some disturbance in the economy of estrogenic substance. [ED. NOTE: These are interesting observations, which may lead to definite conclusions with more confirmatory evidence.]

Trask, Paul and Vignec²¹⁰ state that the appearance of the poliomyelitis virus in the stools of patients with poliomyelitis seems to be characteristic of many strains. The virus is capable of prolonged activity in stools of human beings and is stable in this medium. The virus can be demonstrated in the stools of patients with paralytic or abortive poliomyelitis and in those of convalescent patients.

Paul, Trask, and Gard²¹¹ report that in two of three large urban epidemics of poliomyelitis the virus of the disease has been detected in samples of sewage. In sewage from one of the sites it was found repeatedly. Both sites from which the virus-containing samples were obtained were in the vicinity of isolation hospitals. The authors believe that the findings indicate that this virus can be transported, for short distances at least, through the medium of flowing sewage. [ED. NOTE: This is one of the most important basic considerations in the whole poliomyelitis problem which has been reported in recent years.]

Pathologic Characteristics.—Sabin²¹² reports that examination of the olfactory bulbs by serial sections from human beings with poliomyelitis does not reveal the pathologic changes which have been observed in the olfactory bulbs of monkeys succumbing after nasal instillation of the virus. No virus was found in olfactory bulbs from 5 patients in whom the virus was isolated from other tissues. This is strong evidence against the theory that the olfactory pathway is the usual portal of entry of the virus in man. [ED. NOTE: From this evidence and his other experimental work Sabin believes that the alimentary tract is one of the main portals of entry of the virus.]

Experimental Poliomyelitis.—Lillie and Armstrong²¹³ report that intracerebral inoculation of cotton rats and white mice with the Lansing strain of poliomyelitis virus produces an inflammatory process char-

210. Trask, J. D.; Paul, J. R., and Vignec, A. J.: *Poliomyelitis Virus in Human Stools*, J. Exper. Med. **71**:751-763 (June) 1940.

211. Paul, J. R.; Trask, J. D., and Gard, S.: *Poliomyelitis Virus in Urban Sewage*, J. Exper. Med. **71**:765-777 (June) 1940.

212. Sabin, A. B.: *Olfactory Bulbs in Human Poliomyelitis*, Am. J. Dis. Child. **60**:1313-1318 (Dec.) 1940.

213. Lillie, R. D., and Armstrong, C.: *Cerebrospinal Pathology of Experimental Poliomyelitis in Eastern Cotton Rat, Sigmodon Hispidus, and in White Mouse, Mus Musculus*, Pub. Health Rep. **55**:718-725 (April 26) 1940.

acterized by necrosis of nerve cells, exudation of polymorphonuclear leukocytes and invasion of necrotic cells, neuronophagia by macrophages, diffuse and focal cellular gliosis, vascular endotheliosis and lymphocyte infiltration of the perivascular sheath. In the brain the dorsal portion of the pons shows the greatest involvement: then the medulla, the mid-brain, the thalamus and the nuclei of the cerebellar roof. The cerebral cortex in both species shows relatively little involvement, mostly in the hippocampus. The corpora striata and cerebellar cortex show the least involvement. Despite intracerebral inoculation into the thalamomesencephalic region the earliest observed lesions are found in the spinal cord in both species. The process is considered closely analogous to the reaction of poliomyelitis in man and in the monkey. In general the amount of lymphocyte infiltration of the perivascular sheath is less in cotton rats than in mice, monkeys or human beings. [Ed. NOTE: This is an excellent article and certainly a real contribution to the subject.]

Armstrong²¹⁴ has accomplished thirteen successive transfers of the virus to white mice. The virus has a tendency to affect a higher proportion of mice in the later transfers. The incubation period is still variable, ranging from two to twenty days, but in the majority of the mice paralysis develops in from three to seven days. Death is now the rule in one to three days from the onset of the symptoms. In the absence of respiratory involvement, the mice attempt to eat, appear sleek and are often without symptoms other than the paralysis. The pathologic lesions in cotton rats and in mice as far as studied are similar in type to those observed in poliomyelitis in other experimental animals and in men. [Ed. NOTE: This is another important experimental contribution.]

Peers²¹⁵ briefly describes the lesions produced in 11 monkeys by the Lansing strain of poliomyelitis virus before transfer to the cotton rat.

After transfer and during its propagation in rats the virus has been reinoculated into 4 monkeys. In these it produced uniform lesions morphologically indistinguishable from those observed before rat passage. It therefore appears that neither the initial transfer nor the subsequent passage through 33 cotton rats visibly modified the pathogenic properties of this strain of poliomyelitis virus.

Toomey²¹⁶ produced paresis of the muscles about the fetlock joints and hoofs of the hindlegs of a horse after injections of fortified virus. Steppage gait developed, and the animal later had difficulty in walking. Its condition gradually became worse, and finally the muscles of the

214. Armstrong, C.: Studies on Choriomeningitis and Poliomyelitis (James M. Anders Lecture), Tr. & Stud., Coll. Physicians, Philadelphia 8:1-11 (April) 1940.

215. Peers, J. H.: Note on Pathology in Monkeys of Lansing Strain of Poliomyelitis Virus Before and After Passage in Cotton Rat, Pub. Health Rep. 55:726-727 (April 26) 1940.

216. Toomey, J. A.: Experimental Poliomyelitis in Animals Other Than the Monkey: Review of Literature, J. Pediat. 16:519-527 (April) 1940.

hindlegs as well as those of the hoofs were involved. There was difficulty in rising, and its legs spread apart when it was placed on its feet. These experiments suggest to the author the following questions: Can the lower animals harbor the virus? Can they serve as carriers of the infection? Is the disease produced in them different from that occurring in man and in the monkey? Why are the smaller animals more resistant to the disease?

Toomey's²¹⁷ experiments with injections of poliomyelitis virus into the adrenal glands of monkeys lend support to the belief (1) that ordinarily the virus does not spread along well myelinated nerves of healthy *Macaca mulatta* monkeys and (2) that the virus will spread along the nerves of monkeys deficient in vitamin D if the virus is simply placed in contact with postganglionic fibers. The presumption is that in the latter animals the preganglionic medullated nerve fibers to the adrenal gland are made deficient and hence more susceptible.

Schultz²¹⁸ gives the results of his experiments with chemical agents in the prevention and treatment of experimental poliomyelitis. He states that

artificially induced acceleration of the metabolism, the administration of such substances as vitamin B, viosterol and antuitrin S [chorionic gonadotropin]; of sulfanilamide, sodium sulfanilsulfanilate and sulfapyridine; also of several medicinal dyestuffs, used for their possible modifying action on the nervous pathways, all have failed to exercise any discernible therapeutic effect though the treatments were started a day or two after the inoculation of the animals and were continued until paralysis appeared.

[ED. NOTE: These are interesting observations, which should be borne in mind in treating the disease in its acute stage, but do not confirm the clinical observations of Rhett.²¹⁹]

Examination.—Lowman²²⁰ describes the tests used in his clinic for testing muscle groups. His conclusions are as follows:

These methods of recording muscle group strengths are time-saving in a busy clinic, as the surgeon can quickly determine the imbalances and can quickly visualize joint function and control, which is what he is most concerned with in mapping his plan for reconstructive surgery. Clinically they are sufficiently accurate to meet the needs of the medical attendant and technicians. Every person using these scales can obtain about the same picture of the patient's condition. Uncertainties in the minds of everyone involved are minimized because no two persons can properly and equally evaluate all the complex muscle actions which take place mainly by groups. In

217. Toomey, J. A.: Absorption of Poliomyelitis Virus by Possibly Deficiently Medullated Nerves, *Am. J. Dis. Child.* **60**:548-551 (Sept.) 1940.

218. Schultz, E. W.: Chemical Agents in Prevention and Treatment of Experimental Poliomyelitis, *Am. J. Pub. Health* **30**:175-179 (Feb.) 1940.

219. Rhett, W. M.: Prophylaxis and Treatment of Poliomyelitis with Neoprontosil, *J. Pediat.* **16**:326-336 (March) 1940.

220. Lowman, C. L.: Muscle Strength Testing, *Physiotherapy Rev.* **20**:69-71 (March-April) 1940.

checking the whole body there are about 105 items if separate muscles are graded, whereas the chart for the above check has about 50, so that saving in time in making the check is also worth consideration.

[ED. NOTE: This is a good article and should be read by every one treating these conditions. It would be most advisable and helpful to all if some uniform system of muscle testing and recording could be adopted.]

Treatment.—Rhett ²¹⁹ states that there is no way of making a diagnosis of poliomyelitis in the absence of involvement of the central nervous system. In an attempt to determine the value of azosulfamide (disodium 4-sulfamidophenyl-2'-azo-7'-acetyl-amino-1'-hydroxynaphthalene-3',6'-disulfonate) as a prophylactic and therapeutic agent in clinical poliomyelitis, it was given to 440 acutely ill children during an epidemic in an approximate dose of 1 grain (0.06 Gm.) per pound (0.45 Kg.) of body weight per day. In this series paralysis developed in 1 child; this occurred when the dose was reduced below the maintenance level. The paralysis subsided completely in three weeks. Two children had meningeal symptoms when the dose was diminished below this same maintenance level, and these symptoms subsided when the full dose was given again. Eleven additional patients with paralytic involvement were treated during the same period. Toxic symptoms subsided within twenty-four to forty-eight hours, and there was no apparent advance in paralytic involvement after the doses reached adequate amounts and were maintained for twenty-four to forty-eight hours. Rhett states: "It is difficult to avoid the feeling that the drug is clinically effective in inhibiting the virus of poliomyelitis." [ED. NOTE: Grants have been made by the National Foundation of Infantile Paralysis to evaluate the effect on poliomyelitis of the various chemotherapeutic agents, including sulfanilamide and its derivatives. No favorable reports on the value of these agents have as yet been made.]

Thenebe and Hirshberg ²²¹ report their experiences with 27 consecutive patients with preparalytic infantile paralysis (36.4 per cent of the total patients admitted) treated with nonspecific protein (sterile milk given intramuscularly), 50 per cent sucrose solution given intravenously and dehydration (restricted intake). There was no paralysis or death in this group. In 1 case weakness developed, which subsequently disappeared entirely before the patient was discharged from the hospital.

Operative Treatment.—King ²²² reports:

One hundred and six ankle fusions were done in a five year period (1934 to 1938 inclusive) on patients with residual anterior poliomyelitis at the New York

221. Thenebe, C. L., and Hirshberg, M. S.: Further Studies in Therapy of Acute Anterior Poliomyelitis, Connecticut M. J. 4:25-27 (Jan.) 1940.

222. King, B. B.: Ankle Fusion for Correction of Paralytic Drop Foot and Calcaneus Deformities, Arch. Surg. 40:90-97 (Jan.) 1940.

Orthopaedic Dispensary and Hospital. Of these, 72 were done for paralytic drop foot and 34 for paralytic calcaneus deformities. The patients have been carefully followed, the follow-up period ranging from seven months to five and one-half years. In 85 cases (80 per cent) the end result was good. In 10 (9 per cent) the end result was only fair, there being either too much or too little equinus. In 5 (5 per cent) the end result was good so far as the ankle was concerned but an associated unstable knee was not rendered stable. In 6 (6 per cent) the end result was good so far as the ankle was concerned but an associated lateral instability of the foot needed further operative stabilization of the subtalar and midtarsal joints. In no case were the results considered poor. Of 32 unstable knees, 27 (84 per cent) were stabilized by ankle fusion. There was no resulting interference with growth in any case. Functional use of the involved extremity was improved in all cases. In 4 cases (4 per cent) pseudarthrosis developed, but in all 4 of these the joint became solidly arthrodesed after refusion.

Ankle fusion is a satisfactory method of treating drop foot and calcaneus deformities regardless of the cause. It results in freedom from disability caused by deformity, pain or instability. In a fused ankle there is no pain, body impingement or swelling such as occurs at times after bone block operations. The operative procedure is relatively simple in contrast to such methods as the Lambrinudi operation and its modifications. An additional advantage is that associated instability of the knee can often be corrected by ankle fusion. The end results are uniformly satisfactory as indicated by this five year study of 106 cases.

It is important to avoid injury to the epiphyseal cartilages of the distal ends of the tibia and fibula if they are still present. The end result is determined by the degree of equinus obtained. Five degrees to 10 degrees of equinus for males, and 10 to 15 degrees of equinus for females is in general satisfactory.

[ED. NOTE: This is a carefully prepared report of a procedure which we believe is not performed in many clinics for either a paralytic calcaneus or drop foot.]

For tibial torsion following deformities of the foot resulting from poliomyelitis and requiring osteotomy for correction, O'Donoghue²²³ performs a Z osteotomy and in addition removes a triangular wedge longitudinally to obtain correction. [ED. NOTE: Technically this looks good. However, is not a simple osteotomy all that is necessary to correct this deformity?]

VIII. NEUROMUSCULAR DISORDERS, EXCLUSIVE OF INFANTILE PARALYSIS

General Considerations.—Under the heading of neuromuscular disorders are grouped the many types of degenerative changes in the neuromuscular system: dystrophy, muscular atrophy, amyotonia, myasthenia and like conditions. Terminology presents a great difficulty. So many apparently different entities having at the same time so many

223. O'Donoghue, D. H.: Controlled Rotation Osteotomy of Tibia, *South. M. J.* 33:1145-1149 (Nov.) 1940.

common characteristics are included that it is extremely confusing to try to develop a satisfactory classification for use in a review of the literature.

Pseudohypertrophic Muscular Dystrophy.—There has been great interest in the use of vitamin therapy to bring about a slowing down at least of the progress of pseudohypertrophic muscular dystrophy. A nonspecific nutritional muscular dystrophy has been produced in rabbits by a diet deficient in vitamin E, and Mackenzie and McCollum²²⁴ describe the cure of this condition by the use of synthetic vitamin E in the form of alpha tocopherol. This compound has been subjected to extensive investigation in the last year by a number of the better pharmaceutical concerns. It has the advantage over wheat germ oil that it can be more definitely standardized as to dosage. Encouraging results were obtained by Bicknell,²²⁵ and work similar to that of Mackenzie and McCollum²²⁴ was carried out by Shimotori²²⁶ with satisfactory results in guinea pigs. On the other hand, Antopol and Schotland²²⁷ treated pseudohypertrophic muscular dystrophy with vitamin B₆ (pyridoxine) and obtained some control over the condition. Donovan²²⁸ combined the use of the vitamin B complex and vitamin E and also gained satisfactory results.

It appears from the literature that the particular constituent of the vitamin B complex which is helpful in treating these conditions is vitamin B₆ (given in the form of pyridoxine hydrochloride) and that the use of this compound in connection with the tocopherols, whether alpha tocopherol alone or a combination of alpha, beta and gamma tocopherol, produces the results. It is believed by many that both vitamin B₆ and vitamin E are necessary and that neither alone is entirely effective.

Hypertrophic Muscular Dystrophy (Hypertrophia Musculorum Vera).—Hypertrophic muscular dystrophy appears in adults and is not common; it is believed to be in some way associated with thyroid

224. Mackenzie, C. G., and McCollum, E. V.: Cure of Nutritional Muscular Dystrophy in Rabbit by Alpha-tocopherol and Its Effect on Creatine Metabolism, *J. Nutrition* **19**:345-362 (April) 1940.

225. Bicknell, F.: Vitamine E in Treatment of Muscular Dystrophies and Nervous Diseases, *Lancet* **1**:10-13 (Jan. 6) 1940.

226. Shimotori, N.; Emerson, G. A., and Evans, H. M.: Prevention of Nutritional Muscular Dystrophy in Guinea Pigs with Vitamine E, *J. Nutrition* **19**:547-554 (June) 1940.

227. Antopol, W., and Schotland, C. E.: Use of Vitamin B₆ in Pseudohypertrophic Muscular Dystrophy, *J. A. M. A.* **114**:1058-1059 (March 23) 1940.

228. Donovan, G. E.: Lordosis and Muscular Dystrophy, *Lancet* **2**:162-163 (Aug. 10) 1940.

insufficiency. Hesser²²⁹ has reported a case in which this condition was associated with hypothyroidism. Mollaret and Sigwald²³⁰ point out the relation between acquired generalized muscular hypertrophy and thyroid insufficiency. The latter would suggest a glandular relation to muscular hypertrophy as differentiated from pseudohypertrophy which apparently may be associated with vitamin deficiency.

Progressive Muscular Atrophy.—There is little in the literature concerning progressive muscular atrophy other than that in certain instances it may be in some way congenital. There is no proof of any hereditary factor, but the report by Ruggeri²³¹ of muscular atrophy with other changes in 2 brothers and a sister is interesting, since in this instance the condition does not appear to be sex linked.

Amyotrophic Lateral Sclerosis.—Hassin²³² points out that amyotrophic lateral sclerosis is usually not difficult to diagnose. However, he shows that there are often cases in which a number of the ordinary clinical manifestations are lacking. In these cases incorrect diagnosis is frequent, since the picture may suggest other diseases. However, in his cases pathologic study proved the nature of the disease. In 1 of the cases the clinical picture was suggestive of spastic paraplegia of the Charcot-Erb type. He points out that there may be loss of tendon reflexes in the presence of a degenerative pyramidal tract. This of course is true. The loss of tendon reflexes sometimes occurs with other conditions in which there is degeneration of the pyramidal tract, such as certain types of cerebral spastic paralysis due to other causes.

Wechsler²³³ reports a recovery obtained by treatment with the tocopherols (vitamin E).

Myasthenia Gravis.—In reviewing the literature on myasthenia gravis, Levy²³⁴ indicates the many possible causes. According to Fraser

229. Hesser, F. H.: Hypertrophia Musculorum Vera (Dystrophia Musculorum Hyperplastica) Associated with Hypothyroidism: Case Study, *Bull. Johns Hopkins Hosp.* **66**:353-377 (June) 1940.

230. Mollaret, P., and Sigwald, J.: Acquired Generalized Muscular Hypertrophy and Thyroid Insufficiency in Adult with Report of Case, *Gaz. méd. de France* **47**:165-168 (April 1) 1940.

231. Ruggeri, R.: Acromicria and Muscular Atrophy in Two Brothers and Sister with Cleidocranial Dysostosis, *Endocrinol. e pat. costit.* **15**:52-65 (Feb.) 1940.

232. Hassin, G. B.: Amyotrophic Lateral Sclerosis: Anatomic and Pathologic Considerations, *Arch. Neurol. & Psychiat.* **43**:765-777 (April) 1940.

233. Wechsler, I. S.: Recovery in Amyotrophic Lateral Sclerosis Treated with Tocopherols (Vitamin E): Preliminary Report, *J. A. M. A.* **114**:948-950 (March 16) 1940.

234. Levy, M. L.: Symposium on Neuropsychiatry: Myasthenia Gravis, *Med. Rec.* **151**:269-273 (April 17) 1940.

and Pritchard,^{234a} the preponderance of evidence favors the curare-like poisoning hypothesis. Disturbance of the creatine-creatinine relation similar to the metabolic upset in muscular dystrophy was believed by some observers to be a factor. While it can be stated that the myoneural junctions are certainly involved, they are probably not the only site of physiologic disturbance in the neuromotor system.

The use of prostigmine followed by the administration of aminoacetic acid and ephedrine has proved satisfactory. It is recommended that the simultaneous daily administration by mouth of aminoacetic acid and prostigmine methylsulfate be given further trial as standard therapy for patients with myasthenia gravis. Levy recommends the concurrent use of the drugs and advises the oral administration of 12 Gm. of aminoacetic acid and 30 to 60 mg. of prostigmine methylsulfate per day. Scannell²³⁵ presents substantiating evidence for the use of these drugs. In a paper by Morgan and Williams²³⁶ myasthenia (though not myasthenia gravis) is discussed in its relation to thyrotoxicosis. Four cases were reported; in 2 the patients recovered after thyroidectomies. One patient died while being prepared for thyroidectomy, apparently from exhaustion of the muscles of respiration. The fourth case was too recent to report. The relation between myasthenia and thyrotoxicosis is also discussed by van Bogaert;²³⁷ in the case he reports there was the still further complication of diabetes mellitus.

Dystonia Musculorum Deformans.—Lemere²³⁸ discusses the quinine treatment of dystonia musculorum deformans. He believes that results from the use of quinine support the contention of Hassin^{238a} that dystonia musculorum deformans is due to a disturbance of muscular tone and not to a central lesion. The case Lemere reports is that of a woman with dystonic motions chiefly in the neck; there was a remarkable response to the use of quinine up to the point of cinchonism.

[Ed. NOTE: The group of neuromotor conditions just discussed is variegated and represents several different entities; this is shown by the

234a. Fraser, F. R.: Transmission of Nervous Effects by Acetylcholine, Brit. M. J. **1**:1349-1354 (June 25) 1938. Pritchard, E. A. B.: Prostigmin in Myasthenia Gravis, Lancet **1**:432-434 (Feb. 23) 1935.

235. Scannell, R. C.: Myasthenia Gravis: Case with Necropsy, J. Iowa M. Soc. **30**:154-159 (April) 1940.

236. Morgan, H. J., and Williams, R. H.: Muscular Atrophy and Weakness in Thyrotoxicosis (Thyrotoxic Myopathy, Exophthalmic Ophthalmoplegia), South. M. J. **33**:261-269 (March) 1940.

237. van Bogaert, L.: Antagonism of Myasthenia Gravis and Thyrotoxicosis, Schweiz. med. Wchnschr. **70**:501-502 (June 8) 1940.

238. Lemere, F.: Quinine Treatment of Dystonia Musculorum, J. A. M. A. **114**:1068 (March 23) 1940.

238a. Hassin, G. B.: Quinine and Dystonia Musculorum Deformans, J. A. M. A. **113**:12 (July 1) 1939.

diversity of response to various forms of treatment. In some cases recovery was obtained by the use of vitamin therapy; in others, by glandular therapy; in still others by the use of prostigmine and amino-acetic acid, and in Lemere's case quinine seems to have been effective. There is room for considerable advance in the study of both the causation and the treatment of these conditions, but what is most needed is a basis for a more definite and accurate classification of the components of this rather heterogeneous group.]

Traumatic and Other Acutely Acquired Paralysis.—[ED. NOTE: At the present time, because of the greatly increased number of injuries, the literature on the treatment of traumatic paralysis is extensive. The subjects discussed are paralysis resulting from injuries from automobiles and airplanes and paralysis resulting from occupational conditions; the latter variety is complicated by hysteria and difficulties about compensation.]

Many reports deal with methods of nerve suture; among these the work of Dunn²³⁹ in comparing various methods of nerve suture is of interest.

Forrester²⁴⁰ makes a plea for the early suture of nerves. He also discusses detailed technics, describes common injuries of nerves and gives a number of case reports.

Paralysis of the serratus anterior muscle is discussed by Overpeck and Ghormley.²⁴¹ In their series of cases the causative agent was trauma in 82 per cent. Treatment was of two general types, conservative and operative. In the conservative type of treatment there was complete recovery in a number of instances. Of the operative types of treatment there were three general methods: (1) fixation of the scapula to the underlying ribs, (2) substitution of an adjacent subscapular nerve for the long thoracic and (3) use of transplants of the various muscles of the shoulder girdle.

McGoogan²⁴² reports 3 cases of isolated paralysis of the serratus anterior muscle during the puerperium. In all instances this occurred on the fourth day after delivery. The cause could possibly have been tilting of the head and neck while the patient was under the anesthesia,

239. Dunn, G. R.: Symposium on Fractures and Other Trauma: *Peripheral Nerve Surgery*, Minnesota Med. 23:748-751 (Oct.) 1940.

240. Forrester, C. R. G.: *Peripheral Nerve Injuries with Results of Early and Delayed Suture*, Am. J. Surg. 47:555-572 (March) 1940.

241. Overpeck, D. O., and Ghormley, R. K.: *Paralysis of Serratus Magnus Muscle, Caused by Lesions of Long Thoracic Nerve*, J. A. M. A. 114:1994-1996 (May 18) 1940.

242. McGoogan, L. S.: *Isolated Paralysis of Serratus Anterior Muscle During Puerperium*, Am. J. Obst. & Gynec. 40:313-315 (Aug.) 1940.

but McGoogan inclines more strongly to the view that it represented a deficiency of members of the vitamin B complex during the puerperium.

A complete, exhaustive and well illustrated report of traumatic lesions of the nerves of the wrist is made by Harmer.²⁴³ [ED. NOTE: This article is of great value and covers all phases of the diagnosis and the treatment of these conditions.] Munro and Wegner²⁴⁴ and Stuck²⁴⁵ discuss in considerable detail wounds and injuries with and without bone or nerve damage in the cervical region as well as in the lower part of the spinal cord.

Nerve Paralysis Due to Toxic Agents.—Rolleston²⁴⁶ reports a case of hemiplegic paralysis following diphtheria. Valerio²⁴⁷ reports 2 cases of brachial paralysis following the use of antigonococcic serum. Camaüer²⁴⁸ reports paralysis of the left axillary nerve following the administration of antitetanic serum.

Holtzman and Howes²⁴⁹ report destruction of peripheral nerves by the action of radium. In their case, paralysis came on during the course of reaction to irradiation. The latent period of one week between the application of the needles and the onset of paralysis eliminated any mechanical injury by the radium needles as a cause. The destruction of the nerve by neoplastic invasion could be ruled out by the disappearance of the nodule treated concomitantly with the onset of paralysis. The authors do not think that paralysis was the direct result of irradiation of the nerve tissue itself; they consider it rather the result of the formation of scar tissue. They feel that this secondary obliteration of the nerves should be anticipated and intensive therapy applied to the areas affected.

[ED. NOTE: These cases serve to emphasize the occasional dangers to the nervous system from the use of serum and other toxic agents.]

243. Harmer, T. W.: Traumatic Lesions of Nerves of Wrist and Hand, *Am. J. Surg.* **47**:517-541 (Feb.) 1940.

244. Munro, D., and Wegner, W.: Bone Lesions Accompanying Cervical Spinal Cord Injuries: End Result Study of Seventy-Six Cases, *New England J. Med.* **222**:167-173 (Feb. 1) 1940.

245. Stuck, R. M.: Spinal Injuries with Nerve Damage, *Southwestern Med.* **24**:157-160 (May) 1940.

246. Rolleston, J. D.: Hemiplegia in Diphtheria, *Clin. J.* **69**:67-68 (March) 1940.

247. Valerio, A.: Two Cases of Postantigonococcic Serum Brachial Paralysis, *Urol. & Cutan. Rev.* **44**:294-295 (May) 1940.

248. Camaüer, A. F.: Paralysis (Inflammation of Left Circumflex Nerve) After Use of Tetanus Antitoxin: Case Report, *Prensa méd. argent.* **27**:548-550 (March 13) 1940.

249. Holtzman, I. N., and Howes, W. E.: Peripheral Nerve Destruction: Unusual Sequel of Radium Therapy, *Am. J. Roentgenol.* **43**:426-427 (March) 1940.

Tabes Dorsalis and Syringomyelia.—Soto-Hall and Haldeman²⁵⁰ discuss neuropathic joint disease (Charcot joint). They say that the diagnosis of this disease rests on observation of a swollen, relaxed and disorganized joint, comparatively painless, in cases in which the usual signs of tabes dorsalis, syringomyelia or other involvement of the spinal cord are presented. The authors report 40 cases of various types of the disease and believe that the clinical evidence of rigid pupils and absence of knee jerks is of greater importance in the diagnosis of tabetic arthropathy than are tests of the blood and the spinal fluid. They feel that a culture of the synovial fluid should be made prior to any operative procedure on a Charcot joint.

McCauley²⁵¹ reports operative treatment of neurotrophic joints. He feels that when there is involvement of the spine operative fusion should be attempted in early stages, but that once extensive destruction has occurred this procedure is not advisable. He reports that support of the hip joint by means of braces is usually better than arthrodesis. The latter is more satisfactory in involvement of the various joints of the foot. It is important that routine periodic examinations be made of the lower extremities to discover the condition as early as possible so that arthrodesis may be successfully utilized.

Conley and Miller²⁵² report 5 cases of atrophic Charcot hip and conclude that this condition is not so uncommon as generally supposed. They believe the diagnosis should be suspected when there is increased mobility of the joint with a positive Wassermann reaction of the blood or spinal fluid. [ED. NOTE: A number of other cases of isolated Charcot joint have been reported during the year. Occurrence seems about evenly divided between unilateral and bilateral involvement.]

Cerebral Palsy.—Practically all the literature on cerebral palsy is devoted to statistical analysis, treatment and laboratory study of the various types. Making a statistical analysis, Phelps²⁵³ reports approximately 68.8 per cent of a large series of patients as of essentially normal intelligence. This checks well with the school placement, since retardation of three grades in school represents approximately the retardation due to the handicap. He reports that in 57 per cent of the cases the cerebral palsy is quadriplegic; in 21 per cent, hemiplegic; in 11 per cent,

250. Soto-Hall, R., and Haldeman, K. O.: *Diagnosis of Neuropathic Joint Disease (Charcot Joint): Analysis of Forty Cases*, J. A. M. A. **114**:2076-2078 (May 25) 1940.

251. McCauley, J. C., Jr.: *Operative Treatment of Neurotrophic Joints*, Urol. & Cutan. Rev. **44**:592-594 (Sept.) 1940.

252. Conley, A. H., and Miller, D. S.: *Atrophic Charcot Hips: Report of Five Cases*, J. Bone & Joint Surg. **22**:638-644 (July) 1940.

253. Phelps, W. M.: *Treatment of Cerebral Palsies*, J. Bone & Joint Surg. **22**:1004-1012 (Oct.) 1940.

paraplegic; in the remainder, scattered in various combinations. The cases in which there is true spasticity represent 54 per cent of the total; athetosis is present in 40 per cent and ataxia in only 5 per cent. The incidence of the condition is entirely predictable, since the number of cases found per hundred thousand of population is the same for all the various areas of the country studied. Operation is limited to the truly spastic type and is not indicated for the athetoid. Sirkin²⁵⁴ reports a critical analysis of five years' work with cerebral palsy in the New York State School, for mentally defective children, at Newark, New York. [ED. NOTE: This report is especially interesting in that all of these children, who are definitely of low intelligence, succeeded in making satisfactory physical progress and thereby became much less of a social problem to the institution.]

With regard to the various methods of treatment, the question of the use of curare is discussed by Burman.²⁵⁵ He states that "curare is a variable mixture, so that it is difficult to get a curare of constant assay and constant action for use in dystonic and spastic states." He investigated two erythrina derivatives, erythroidine hydrochloride (an alkaloid extracted from *Erythrina americana* mill) and extract of *Erythrina glauca*, as well as a number of curare extracts. He observed in general that any preparation of curare after its intravenous injection exerted its effects first on the muscles supplied by the cranial nerves, then on skeletal muscles and lastly on the muscles of respiration. The initial symptom is invariably dizziness. As this recedes, the upper eyelids become heavy and may droop temporarily. Diplopia may be present. As these changes increase, the skeletal release begins to take place, resulting in cessation of athetosis, plastic rigidity or hypertonia. The effect is not long lasting; the patient returns to normal within twenty to thirty minutes. It is hoped that a safe curare of prolonged effect will be found, one which will be effective when orally administered.

Bennett²⁵⁶ reports the use of curare in preventing traumatic complications in convulsive shock therapy. [ED. NOTE: This has no direct relation to cerebral palsy, but the results of this use of the drug could be studied to obtain greater familiarity with its effects.]

Pusitz, Lattimore, Gold and Ebendorf²⁵⁷ also report biologic and chemical studies with the use of curare.

254. Sirkin, J.: Five Years Work with Cerebral Palsy: Critical Analysis, *Psychiatric Quart.* **14**:185-193 (Jan.) 1940.

255. Burman, M. S.: Clinical Experiences with Some Curare Preparations and Curare Substitutes, *J. Pharmacol. & Exper. Therap.* **69**:143-148 (June) 1940.

256. Bennett, A. E.: Preventing Traumatic Complications in Convulsive Shock Therapy by Curare, *J. A. M. A.* **114**:322-324 (Jan. 27) 1940.

257. Pusitz, M. E.; Lattimore, J. L.; Gold, J. L., and Ebendorf, H.: Biologic and Biochemical Studies of Curare: Preliminary Report, *J. Kansas M. Soc.* **41**: 374-379 (Sept.) 1940.

Stieda²⁵⁸ discusses the question of the value for Little's disease of the Bulgarian treatment with belladonna. The treatment is of some value, but it seems probable that the effects obtained were on those patients in whom the condition was acquired rather than due to a birth injury or congenital. [ED. NOTE: It appears that the use of these various drugs brings about a release of latent abilities such as would be found in postencephalitic conditions.]

Neuromotor Research.—Carey²⁵⁹ reports a study of the wave mechanics of smooth muscle action, which is discussed in a series of articles on this general subject. Experimental multiple reflections between intestinal ligatures transformed traveling micropressure waves in smooth muscle into stationary ones. This smooth structural wave change has the typical attribute of a longitudinal wave of compression. "The living matter of the cytoplasm of smooth muscle, therefore, seems to have two aspects, namely (1) colloidal particle and (2) the associated micropressure wave."

Rosenblueth and Cannon²⁶⁰ describe conditions affecting the late stages of neuromuscular transmission in relation to certain conditioning factors. Administration of prostigmine has been found to change the relation between stage 4 (fatigue) and stage 5 (recovery while tetanic stimulation is continued). Although curare has a prompt depressive influence in stage 4, its effect is less profound and less persistent than in fresh muscle; this shows that the fatigued synapse is more resistant to curare than the fresh one. Hoefer and Putnam²⁶¹ discuss action potentials of muscles in spastic conditions, athetosis, Sydenham's chorea, rigidity and tremor. The authors present characteristic recordings of these various conditions and say these may be definitely identified as the particular type of reaction to be expected. Putnam²⁶² reports recent advances in diagnosis and treatment of alternating tremor (paralysis

258. Stieda, H.: Question of Value of Bulgarian Cure with Homburg 689 (Belladonna Preparation) in Little's Disease, *Med. Klin.* **36**:191-192 (Feb. 16) 1940.

259. Carey, E. J.: Wave Mechanics of Smooth Muscle Action: Experimental Multiple Reflections Between Intestinal Ligatures Transform Traveling into Stationary Micropressure Waves in Smooth Muscle, *Arch. Path.* **29**:321-344 (March) 1940.

260. Rosenblueth, A., and Cannon, W. B.: Some Features of Early Stages of Neuromuscular Transmission, *Am. J. Physiol.* **130**:219-229 (July) 1940.

261. Hoefer, P. F. A. and Putnam, T. J.: Action Potentials of Muscles in "Spastic" Conditions, *Arch. Neurol. & Psychiat.* **43**:1-22 (Jan.) 1940; Action Potentials of Muscles in Athetosis and Sydenham's Chorea, *ibid.* **44**:517-531 (Sept.) 1940; Action Potentials of Muscles in Rigidity and Tremor, *ibid.* **43**:704-725 (April) 1940.

262. Putnam, T. J.: Alternating Tremor (Paralysis Agitans) and Athetosis: Recent Advances in Diagnosis and Treatment, *New England J. Med.* **222**:473-477 (March 21) 1940.

agitans) and athetosis. He states that the standard treatment of paralysis agitans of all types is the administration of drugs of the scopolamine series and that these drugs should always be tried, though the results are often disappointing. He says that administration of scopolamine should be pushed rather rapidly until the patient has toxic symptoms. The Bulgarian belladonna treatment is of questionable advantage over the older forms of therapy but may be tried if the others fail. The effect of drugs of the atropine series is sometimes increased by the auxiliary administration of amphetamine sulfate. This is particularly effective against the tics, such as oculogyric crises, that often complicate the postencephalitic type of the syndrome. He feels that curare at present is too cumbersome and dangerous for routine use.

With regard to treatment by surgical intervention, success has been reported with operations of two general types, resection of the motor or premotor cortex and section of the pyramidal tracts. The more extensive cortical operations usually produce monoplegia. For athetosis he states that the method of treatment most commonly used is reeducation of the affected muscles. This method has been reported to yield excellent results, although from the published accounts it is difficult to be sure what part of the improvement was in the associated hemiplegic disturbances. Treatment of this condition by drugs has been uniformly unsuccessful in the past. The use of curare may be beneficial, but many difficulties and dangers are to be overcome before it can be given wide acceptance. In the operative treatment of athetosis, resection of the corresponding motor cortex has brought about relief of the abnormal movements, but cortical monoplegia has resulted. Section of extra-pyramidal tracts in the anterior column of the spinal cord is described, and the results of treatment are reported as favorable.

IX. FRESH FRACTURES AND DISLOCATIONS

Fracture of the Clavicle in Children.—McLaughlin²⁶³ reports his experiences with 700 cases of fracture of the clavicle in children treated at the Presbyterian Hospital in New York during the past few years. When complete fracture of the clavicle occurs, the shoulder falls downward, inward and forward. The medial fragment remains in approximately the normal position; the outer fragment is carried away with the shoulder by its attachment to the scapula. Pain on motion and tenderness are present. The diagnosis may not be obvious with greenstick fractures; in fact, careful examination of the clavicle is always indicated with an injury of the shoulder. Regardless of deformity, the functional

263. McLaughlin, H. L.: Management of Fractured Clavicle in Children. S. Clin. North America 20:549-556 (April) 1940.

results are uniformly good. However, in spite of the tendency of a growing child spontaneously to eliminate gross deformity, this may not disappear if the fracture is left unreduced. The cosmetic result is naturally of greater importance to girls than to boys.

The anesthesia of choice, when anesthesia is necessary, is local infiltration. In reducing a fractured clavicle, the operator places his knee between the scapulas and pulls each shoulder upward, backward and outward. The pull must be gentle, steady and slow. When the length of the clavicle is restored, the grasp on the normal shoulder is relieved, and the free hand is used for direct manipulation of the fragments. The reduction is manually maintained while an assistant applies the splint, which consists either of a well molded plastic material well padded in the axillas or of a clavicular cross. Occasionally, when there are oblique or comminuted fractures, traction is required. The arm is abducted in line with the axis of the clavicle, and skin traction is applied. Splints are usually removed after three weeks and a sling used for support. Complications are rare and consist of compression of the supra-clavicular nerve, nonunion (when interposition of tissue occurs) and compression of the subclavian vessels or axillary nerve trunks. [Ed. NOTE: This review is excellent. There are many methods of treating fractures of the clavicle. The important elements of treatment are fixation and frequent observation. Open reduction is seldom necessary. The effective method of the plaster yoke originally described by Billington has not been sufficiently emphasized. In 1928 one of us (H. E. C.²⁶⁴) described an original adhesive dressing, which has been successfully used for many years on ambulatory patients.]

Operative Fixation of Fractures of the Clavicle.—Murray²⁶⁵ states that with the present methods of fixation for fractures of the clavicle practically all fractures unite, even though the fragments are not in good anatomic position, and that the functional results are good. The cosmetic and anatomic results are frequently disappointing.

To obviate unsatisfactory results he has developed the following method of fixation: When sufficient reduction has been obtained, a $\frac{1}{4}$ inch (0.6 cm.) incision is made 1 inch (2.5 cm.) from the inner end of the clavicle. Through this a hole $\frac{1}{4}$ inch (0.6 cm.) in diameter is drilled in the cortex. The position of the drill is gradually changed from the perpendicular until it points toward the central cylinder. Through this hole a medium-sized Kirschner wire is passed. If started in the right direction, it always travels the central cylinder and passes across the line of fracture into the distal fragment, provided the reduction

264. Conwell, H. E.: Fractures of the Clavicle, J. A. M. A. 90:838-839 (March 17) 1928.

265. Murray, G.: Method of Fixation of Fracture of Clavicle, J. Bone & Joint Surg. 22:616-620 (July) 1940.

is sufficient. The clavicle immediately becomes stable, and the arm, shoulder and clavicle can be moved about freely without displacement of the fragments. The wire is cut short and a small dressing placed over the incision. Later, if necessary for any reason, it can be removed with the area under local anesthesia. No other fixation except a sling is required, and the patient is comfortable. In several cases in which reduction could not be satisfactorily obtained by other means, open reduction was done. During the past three years this method has been used in 29 cases. In each case the fragments have united in good position. There have been no complications or infections in any of these cases. [ED. NOTE: Open reduction is seldom indicated for fracture of the clavicle, and the method described by Murray is to be considered carefully before it is accepted as a routine procedure. One of us (H. E. C.) has seen 2 patients who became infected after this treatment was used.]

Fractures of the Shaft of the Humerus.—Caldwell²⁶⁶ shows that in his hands the use of the hanging cast or of the traction cast for the treatment of fractures of the shaft of the humerus has given a high proportion of good results with least annoyance and discomfort to the patient. The cast consists of plaster applied over stockinet only, reaching from the axilla to the base of the thumb; the elbow is flexed to 90 degrees, and the forearm is in midpronation. A bandage placed around the patient's neck is run through a wire loop incorporated in the cast at the level of the wrist. A series of 108 fractures of the shaft of the humerus is analyzed. Fractures of the surgical neck and supracondylar fractures were not included. In the 108 cases, 25 fractures were located in the upper third of the shaft of the humerus, 62 in the middle third and 21 in the lower third. Fifty-nine patients were treated by the hanging cast method; 22 of these had treatment for varying periods by balanced traction in bed. The results obtained were as follows: good union and function in 85 cases; poor position and good function in 6; poor function in 3; nonunion in 1; delayed union in 4; result not ascertainable in 9. While the hanging cast method was used more often than all other methods combined, the others used were similar in principle, except in 3 cases in which the airplane splint was used. [ED. NOTE: Caldwell was one of the first advocates of the hanging cast, and this is the report of his experiences. It must be observed that he does not use the cast routinely on every type of fracture of the humerus. He states that a knowledge of the application of the hanging cast is required and that it is by no means a panacean treatment.]

Gurd²⁶⁷ presents his method of treatment for fractures of the upper two thirds of the humerus. Briefly, the treatment consists of placing a

266. Caldwell, J. A.: Treatment of Fracture of Shaft of Humerus by Hanging Cast, Surg., Gynec. & Obst. **70**:421-425 (Feb., no. 2 A) 1940.

267. Gurd, F. B.: Simple Effective Method of Treatment of Fractures of Upper Two-Thirds of Humerus, Am. J. Surg. **47**:443-453 (Feb.) 1940.

triangular pad under the axilla with a base which affords abduction of the arm of 15 degrees. The arm, shoulder and thorax are then incorporated in a plaster cast; the forearm is left free and is supported by a sling. The sling is removed in seven to ten days, and active motion of the elbow joint is begun. The cast is removed in two to five weeks; a cravat sling is supplied, and active use of the limb is advised. The method described has been used by the author for twenty years with satisfactory results, although no statistical study of end results has been made. It was not used for fractures of the anatomic neck or of the greater tuberosity of the humerus. [ED. NOTE: This is a much more logical and physiologic treatment for such fractures than the application of a hanging cast. However, both technics are more radical than the use of a plaster spica of the shoulder. When the treatment is used efficiently, however, as good, if not better, results are obtained by the use of the hanging cast or of Gurd's method than by the use of a spica of the shoulder.]

Injuries of the Elbow.—Boyer²⁶⁸ stresses the importance of an accurate diagnosis of any injury of the elbow. Careful physical and roentgen examinations should be made, including determination of the presence or absence of injury to the nerves and of the state of the circulation. In dislocation of the elbow, an accompanying fracture is to be looked for. The dislocation should be reduced without delay. In a posterior dislocation the elbow should be hyperextended, and while a gentle pull is applied to the wrist, the physician should exert forward pressure on the olecranon process. The elbow is immobilized. Later, when mobilization is started, it should be gradual.

With supracondylar fractures, Volkmann's ischemia may occur. If after accurate reduction the circulation is not improved, fasciotomy should be performed. In some cases, when reduction cannot be accomplished by manipulation, traction by insertion of a Kirschner wire into the olecranon process is carried out. Reduction is accomplished by extending the arm with traction and pushing the lower fragment of the humerus forward. The forearm is then flexed and immobilized for three weeks; after this it is put in a sling for three more weeks. If an excess of callus is formed, it should be removed by operation. Whether the head and neck of the radius are removed depends on the severity of the injury. For fractures of the olecranon process with separation, internal fixation is required. With a fracture of the upper part of the shaft of the ulna, one must look for an accompanying dislocation of the radius. [ED. NOTE: The importance and efficiency of traction in severe supracondylar fractures cannot be overemphasized. The repair of the

268. Boyer, B. E.: *Fractures and Dislocations of Elbow*, J. Med. 20:431-432 (Jan.) 1940.

bone and the soft tissues is usually good, and the functional result in most instances is better than after any other treatment.]

Mroz ²⁶⁹ stresses the importance of a neurologic examination of the arm before manipulating fractures about the elbow. Fractures about the elbow are usually accompanied by considerable swelling, depending on the amount of injury to the soft tissues. At times, if swelling is due to internal hemorrhage, it may be necessary to aspirate the mass, especially if this swelling impedes the circulation. This not only controls swelling but makes earlier reduction both safer and easier. For the purpose of discussion the following classification of fractures about the elbow joint is used by Mroz: (1) fractures of the distal end of the humerus, including supracondylar fractures, fractures of the internal condyle, fractures of the external condyle and T fractures; (2) fractures of the radius; (3) fractures of the olecranon process.

The supracondylar fracture is the commonest injury of the elbow and is usually seen in children. Under anesthesia, the arm is hyperextended, increasing the deformity, while at the same time the fragments are manipulated into position. The forearm is then flexed to about 70 or 75 degrees and immobilized with adhesive tape. Roentgenograms are taken both before and after reduction. Physical therapy is instituted as soon as union permits.

In badly comminuted and compound fractures of the elbow, skeletal traction is the treatment of choice. Traction is instituted by inserting a Kirschner wire through the proximal end of the ulna. When sufficient callus is present, a cast is applied.

Fracture of the inner or outer condyle of the humerus is another common injury. If displacement is not great, immobilization is all that is necessary. If displacement is great or impossible to maintain, the application of a beef-bone screw or metal nail is necessary.

For fractures of the head of the radius without much displacement or comminution, Mroz recommends conservative treatment. However, if there are extensive comminutions and displacement, the head of the radius should be removed. For fractures of the olecranon process without separation, manipulation is attempted, and if this is not satisfactory, internal fixation is carried out. To prevent Volkmann's ischemia the author recommends that no encircling bandages be applied and that the patient be closely observed. [ED. NOTE: The importance of early open operation for definitely separated fractures of the olecranon process cannot be overemphasized. Early motion is important, and internal fixation makes this possible.]

269. Mroz, R. J.: Fractures About Elbow Joint, *Illinois M. J.* 77:218-224 (March) 1940.

Brewster and Karp²⁷⁰ confirm the prevailing opinion that the functional end results in the treatment of supracondylar fractures of the humerus in children are uniformly good, even when the fractures are not accurately reduced. A diminution in the carrying angle of the elbow producing cubitus varus is often a sequel to a supracondylar fracture (28 per cent in this series) and may be caused by stimulation of the external epicondylar and capitellar epiphysis due to the fracture. This does not affect the function of the elbow. Fracture of the external condyle in a child is a serious injury and if treated in the conventional manner will result in nonunion and distortion of the elbow in a large percentage of cases. In the presence of even a minor displacement which cannot be completely corrected, open reduction is advised. Separation of the epiphysis of the medial condyle has been considered a minor injury, but if nonunion is to be avoided, open suture is advised. [Ed. NOTE: This is a good article and one worthy of careful study.]

Van Gorder²⁷¹ points out that supracondylar T fracture of the humerus can be reduced in most cases by other means than open operation. The importance of preoperative planning and preparation is stressed, and the kinds and shapes of materials desired for internal fixation are described. By fitting his plates on a skeleton to estimate the lengths of screws, bolts or other materials, he saves much valuable time. During operation on a fracture of this type the patient lies face down while his arm with a small pneumatic tourniquet applied is flexed over an arm board. A posterior midline cutaneous incision is made from 5 inches (12.5 cm.) above the olecranon process to 1 inch (2.5 cm.) below its tip. Skin and subcutaneous tissue are widely separated. The ulnar nerve is gently retracted. The superficial fascia over the triceps muscle is cut in the shape of a tongue, the apex of which is about 4 inches (10 cm.) above the olecranon process. This gives an admirable and safe exposure of the fracture, facilitating reduction and allowing the free use of plates, screws, bolts or wire for fixation. The author illustrates his article with sketches which show many excellent reductions maintained by the ingenious use of internal fixation. [Ed. NOTE: This is an excellent technic and aids greatly in operations on this difficult fracture.]

Jackson²⁷² reports an interesting case of anterior dislocation of the elbow with rupture of the brachial artery. Such a combination of

270. Brewster, A. H., and Karp, M.: Fractures in Region of Elbow in Children: End-Result Study, *Surg., Gynec. & Obst.* **71**:643-649 (Nov.) 1940.

271. Van Gorder, G. W.: Surgical Approach in Supracondylar "T" Fracture of Humerus Requiring Open Reduction, *J. Bone & Joint Surg.* **22**:278-292 (April) 1940.

272. Jackson, J. A.: Simple Anterior Dislocation of Elbow Joint with Rupture of Brachial Artery; Case Report, *Am. J. Surg.* **47**:479-486 (Feb.) 1940.

injuries is extremely rare according to the literature. The patient had good results after reduction of the dislocation and suture of the brachial artery. [ED. NOTE: This is indeed a rare dislocation, and Jackson is to be congratulated on the excellent results obtained.]

Griesemer²⁷³ presents a study of external dislocation of the elbow which indicates that reported cases both of complete and of incomplete external lateral dislocation are infrequent. This type of dislocation is often accompanied by fracture in or about the elbow joint or at a lower level of the forearm. Good results are to be expected if reduction is done early. A ten day old dislocation requires open reduction. If early closed reduction fails, open operation should be performed at once. Extensive lacerations of the skin and swelling of the joint as a rule contraindicate operation, unless the patient is seen within three hours after the accident. Fixation should be maintained in supination with flexion at the elbow to as acute an angle as the swelling permits. It is wise to hospitalize the patient several days for observation. Early active motion is essential in either open or closed reduction to obtain early restoration of joint function. Griesemer reports 6 cases. [ED. NOTE: This is an unusually large series. In these cases, if proper handling is not instituted early, the results are usually poor. Injuries of the nerves, especially of the radial and ulnar nerves, are frequent complications. One of us (H. E. C.) observed an injury of the radial nerve which cleared up without surgical intervention.]

Speed and Boyd²⁷⁴ ably present a study of a series of 62 injuries of the elbow with fracture of the ulna associated with dislocation of the head of the radius (Monteggia fracture). Thirty patients had acute fractures; 10 had compound fractures, and the remaining 32 had old injuries of four weeks' or longer duration. In the treatment of these patients it was found that the closed method is usually unsatisfactory for adults. The treatment of choice was open reduction with internal fixation of the fragments of the ulna with a vitallium plate and replacement of the radial head, made secure by a fascial loop around the neck of the radius. Closed reduction may be used for acute fractures in children. However, accurate replacement of the radial head is difficult and the fracture is apt to recur.

For nonunion of the ulna and dislocation of the radial head, resection of the head and of the neck of the radius combined with an onlay bone graft of the ulna fastened by vitallium screws is recommended. Disturbances of the lower radioulnar articulation have not been of sufficient

273. Griesemer, W. D.: External Lateral Dislocation of Elbow, *Am. J. Surg.* 47:57-70 (Jan.) 1940.

274. Speed, J. S., and Boyd, H. B.: Treatment of Fractures of Ulna with Dislocation of Head of Radius (Monteggia Fracture), *J. A. M. A.* 115:1699-1705 (Nov. 16) 1940.

practical importance to contraindicate resection of the head and the neck of the radius. Injury of the radial nerve is avoided by the anatomic approach described.

Fractures of Both Bones of the Forearm.—Key²⁷⁵ presents 8 cases of fracture of both bones of the forearm in which the fragments were displaced. The ages of the patients ranged from 8 to 60 years. Key concludes that if a satisfactory and stable reduction cannot be obtained at the first attempt open reduction and internal and external fixation should be resorted to if adequate facilities are at hand. For internal fixation he prefers inserting small stainless steel wire loops and sprinkling sterile sulfanilamide powder in the wound. For external fixation long posterior and short anterior wood splints encased in a plaster of paris cast give the best results. The cast extends from the middle of the upper part of the arm to the base of the fingers, with the palm left free for exercise of the thumb and the fingers.

Injuries of the Wrist.—Hyman and Martin²⁷⁶ state that fracture of the radius is not uncommonly complicated by dislocation of the inferior radioulnar joint. They give a classification of such lesions, and discuss the causes, mechanics and pathologic anatomy. They present 25 cases. Immediate treatment consists of reduction after manipulation with the patient under anesthesia induced by gas and oxygen and immobilization in a plaster cast to maintain reduction. When the dislocation of the head of the ulna was anterior, the wrist was fixed in palmar flexion; when the dislocation was posterior, the wrist was fixed in dorsiflexion. In no case was open reduction necessary. Active use of the fingers, shoulder and elbow is to be insisted on after reduction. The cast was retained for four to eight weeks, except in 1 case, in which the shaft of the radius was broken. Removal of the cast was followed by active movements. The prognosis is good for posterior dislocation of the head of the ulna associated with fracture of the shaft of the radius or of the lower 1 inch (2.5 cm.) of the radius and for anterior dislocation of the head of the ulna with fracture of the radial shaft. However, the prognosis is not good for anterior dislocation of the head of the ulna associated with a bad Colles fracture. [ED. NOTE: This is an excellent and timely paper. Too little attention is given to injuries of this kind in the acute stage. They frequently go undiagnosed and cause irreparable damage.]

275. Key, J. A.: Common Problems in Surgical Diagnosis: Treatment of Complete Fractures of Both Bones of Forearm, *S. Clin. North America* 20:1393-1412 (Oct.) 1940.

276. Hyman, G., and Martin, F. R. R.: Dislocation of Inferior Radio-Ulnar Joint as Complication of Fracture of Radius, *Brit. J. Surg.* 27:481-491 (Jan.) 1940.

Fisher and Segal ²⁷⁷ conclude that:

1. Injuries of the carpal bones are frequently missed due to failure of the patient to seek medical attention or to lack of adequate roentgenologic study.
2. The navicular is the most frequently fractured and the lunate the most frequently dislocated bone of the wrist. Radiocarpal dislocation is rare, whereas peri-lunar dorsal dislocation is the most common dislocation of the carpus.
3. Nonunion and secondary changes are due to interference with the blood supply and failure to immobilize early and for an adequate length of time.
4. Prognosis is dependent on early recognition, prompt reduction, and prolonged immobilization.
5. Fresh navicular fractures should be immobilized in the position of dorsiflexion and radial deviation for an eight to twelve week period.
6. Old or neglected cases with nonunion, osteolytic, or arthritic changes should be treated by total excision of the entire navicular followed by early mobilization and physiotherapy.

[ED. NOTE: The authors do not emphasize sufficiently either the treatment for the dislocated lunate bone or the rarity of necrosis.]

Thorndike and Garrey ²⁷⁸ state that among the commonly undiagnosed fractures are those of the carpal scaphoid bone (os naviculare). They have seen 17 patients in a college clinic. Eleven of these had old or previously unrecognized fractures. The incidence is high in young men active in sports in which violent hyperextension of the hand takes place. The standard signs for diagnosis are limitation of motion in extension and radial deviation with tenderness over the anatomic snuff box and on the palmar surface over the tubercle of the bone. One obviously incorrect diagnosis frequently made is that of a sprained wrist. The failure to demonstrate these fractures by roentgenograms, especially in the initial roentgen examination, is frequently mentioned. Better views may be taken with the fist clenched and the fingers resting on the x-ray plate with the palm down in extreme ulnar deviation and extreme pronation. If a true undetected fracture is present and motion is permitted, absorption of the bone occurs along the fracture line, and the fracture becomes more evident in one to two weeks. Rigid rest will halt absorption and allow gradual union to take place. These authors use the anatomic classification of fracture of the carpal scaphoid. Fractures through the tuberosity are extra-articular and always heal in four to six weeks by bony union. Fractures through the middle and proximal third of the body of the scaphoid bone constitute the majority of injuries. Fresh fractures show little or no displacement. Treatment is standard-

277. Fisher, D., and Segal, J.: *Injuries of Wrist*, *Mil. Surgeon* 86:134-142 (Feb.) 1940.

278. Thorndike, A., Jr., and Garrey, W. E.: *Fractures of Carpal Scaphoid*, *New England J. Med.* 222:827-830 (May 16) 1940.

ized, and early diagnosis and effective immobilization are the key to good results. Conversely the motion of five articulating surfaces in frequent movements of the hand is the one certain common cause of absorption. The fragments are best apposed with the wrist in 40 to 50 degrees of extension. Rigid immobilization should be carried out for twelve weeks with an additional four weeks of partial immobilization in a supportive gauntlet. Results of later operative treatment in cases of nonunion have been good. [Ed. NOTE: One of us (H. E. C.) has found that abduction of the hand at the wrist (the Soto-Hall technic) is important in addition to the extension mentioned by these authors. This type of fracture too often goes unrecognized.]

Fractures of the Hand.—McNealy and Lichtenstein²⁷⁹ present a summary of the deformities of the metacarpal bones and the phalanges following fractures of the hand. Although a thorough understanding of the attachment of tendons and the direction and force of their pull is preferable in immobilization of the affected bone, they set forth the general principle of aligning the mobile distal fragment with a less mobile proximal fragment. This rule simplifies the essentials of treatment and relieves one of remembering the mechanisms involved in various displacements. It is applicable to all fractures of the bones of the hand. [Ed. NOTE: Too little attention is given to the early treatment and rigid convalescent care of patients with fractures of the metacarpal bones and the phalanges. This lack of interest is causing too frequent disabilities, which in turn cause considerable economic loss. Such disabilities and economic loss could be prevented by early and proper attention to these simple fractures.]

Fractures of the Acetabulum.—Maynard²⁸⁰ presents an important study of fracture of the acetabulum. The cause is a fall or a blow striking on the greater trochanter and hip region. There are slight flexion, abduction and external rotation of the thigh with not more than $\frac{1}{2}$ inch (1.27 cm.) shortening. There is limitation of motion of the hip. Crepitation may be present. The greater trochanter is posterior and less prominent. The patient is put on a fracture bed or hard bed and treated for shock; 10 to 20 pounds (4.5 to 9.1 Kg.) of longitudinal and lateral traction is applied to the extremity. After a few days, when the patient has recovered from shock, manipulation with the aid of general anesthesia should be done. The hip is manipulated in all directions to break up impaction, if any is present. The thigh is then flexed on the abdomen and the leg on the thigh, each to a right angle or more. Forcible adduc-

279. McNealy, R. W., and Lichtenstein, M. E.: *Fractures of Bones of Hand*. Am. J. Surg. 50:563-570 (Dec.) 1940.

280. Maynard, R. L.: *Reduction of Fractures of Acetabulum with Penetration of Head of Femur into Pelvis: Report of Three Cases*, Rhode Island M. J. 23:150-153 (Sept.) 1940.

tion and internal rotation of the extremity are done against a lateral pull placed as high on the inner aspect of the thigh as possible. The patient is returned to bed, and longitudinal and horizontal traction are continued for four to six weeks. After this he remains in bed two to four weeks longer. Then he uses crutches for about two months. In all of Maynard's cases there was some recurrence of deformity with limitation of adduction, internal rotation and flexion of the hip. There was no shortening of consequence, and only a slight limp was apparent. Functional results were good. [ED. NOTE: Latent changes in the bones about the head of the femur and the acetabulum following trauma should always be looked for, especially with injuries as severe as those described.]

Dislocation of the Hip.—De Yoe²⁸¹ describes a modification in the method of Allis for reducing posterior dislocations of the hip. The patient is anesthetized while lying on his back and is so placed that the buttocks are at the end of the table. An assistant holds the normal leg horizontally, or it may be placed on a small table of the same height as the operating table. The pelvis is now strapped to the table or firmly held there by an assistant. The operator takes the dislocated leg, flexes the thigh; with his back against the end of the table and against the patient's buttocks he then brings the dislocated leg over his shoulder. The operator's shoulder is now under the popliteal space. The knee is flexed, and the back of the patient's calf lies against the operator's chest. With the leg firmly held in this position, the operator lifts upward and bends forward easily, exerting powerful traction on the femur. The dislocating force is thus reversed. With an audible click the head of the femur snaps into the acetabulum, and the motion of the thigh is no longer restricted. It is important to make roentgenograms of the hip before manipulation to determine the presence or absence of associated fractures of the pelvis or femur. [ED. NOTE: This is a unique modification of Allis' technic. The taking of roentgenograms before attempt at reduction is indeed a necessary procedure, especially so far as medicolegal aspects are concerned.]

Walker²⁸² points out that traumatic dislocations of the hip constitute 2 to 5 per cent of all dislocations. The most common cause is a severe blow on the flexed knee. The dislocations are classified as anterior or posterior according to their relation to Nélaton's line, which bisects the acetabulum, and further as high or low, depending on the final resting place of the dislocated head. Posterior dislocations are seven times more common. Associated with dislocation of the hip are considerable shock,

281. De Yoe, L. E.: Suggested Improvement to Allis' Method of Reduction of Posterior Dislocation of Hip, *Ann. Surg.* **112**:127-129 (July) 1940.

282. Walker, W. A.: Traumatic Dislocations of Hip Joint, *Am. J. Surg.* **50**: 545-549 (Dec.) 1940.

trauma of the soft parts and frequently fracture of the acetabular rim. The ligamentum teres femoris and the capsule are always torn. The characteristic position in posterior dislocation is flexion, adduction and internal rotation. The position is relatively fixed. The greater trochanter is above Nélaton's line. In anterior dislocation the leg is in external rotation and abduction. There may be slight flexion and extension. Because of the powerful musculature, general anesthesia is necessary for relaxation. During any manipulative procedure, the sole object is to return the head to its socket along the path it traveled while dislocating. To do this with a minimum of trauma, the head must be disengaged from the soft parts and returned to the acetabulum through the original tear in the capsule. In all methods of reduction, flexion of the thigh to about 90 degrees to relax the Y ligament and bring the head opposite the tear in the capsule is essential. Aseptic necrosis of the femoral head after dislocation has been noted. This is due to loss of blood supply, which is maintained through the ligamentum teres, the capsule and the neck. Thus it is important to be careful in manipulating and immobilizing the extremity. The extremity should be protected from early weight bearing. Other sequelae are myositis ossificans of the capsule and injury of nerves. [ED. NOTE: Necrotic changes of the head of the femur following dislocation and fracture are now more frequently recognized than ever before. As the author states, too early weight bearing by the extremity should never be allowed.]

Fractures of the Neck of the Femur.—Moore and Green²⁸³ report 50 consecutive cases of intracapsular fracture of the neck of the femur which have been followed for one to five years. In this group solid bony union developed in 45 cases, or 90 per cent, and questionable union in 1, or 2 per cent; there was definite nonunion in 4, or 8 per cent. The authors stress the fact that, although the procedure of nailing the hip is not difficult, it is a formidable procedure for the occasional operator to undertake. Early in the series three nails were used, but in the later cases two nails were applied in the upper portion of the neck and two nails in the lower portion. This has an increased stabilizing value. The patient may be up on crutches without weight bearing in a few days, but actual weight bearing is not allowed for six months. [ED. NOTE: Internal fixation of intracapsular fractures has its place and advantages. The Whitman abduction cast is being used less as time goes on. The authors are to be congratulated on their higher percentage of unions. Their percentage, however, is much higher than that reported in the final analysis of the Fracture and Traumatic

283. Moore, A. T., and Green, J. T.: Fractures of Neck of Femur Treated by Internal Fixation with Adjustable Nails: End Result Studies. *South. Surgeon* 9:684-689 (Sept.) 1940.

Committee of the American Academy of Orthopaedic Surgeons²⁸⁴ for this or other methods of internal fixation.]

Speed²⁸⁵ states that in fractures of the neck of the femur in the aged a change in the axis leads to changed mechanics of support, often followed by early absorptive changes in the bone. The rule of treatment must be (1) reduction with the patient under proper anesthesia, (2) fixation by operation and (3) appropriate after care.

Proper preoperative treatment is essential. Shock should be treated and a fluid balance established. A gentle and yet thorough physical examination should be made. Before operation temporary fixation by means of traction is advised. Any pathologic condition should be treated. For the anesthetic Speed prefers nitrogen monoxide and oxygen or ethylene; for a second choice he favors local infiltration of procaine hydrochloride.

Fixation may be secured by a Smith-Petersen nail, finer pins or a combination of nail and bone transplant. The last is the method of choice for fractures which have existed for three months without union.

The author states that the percentage of early deaths after operation is not more than 1 when the treatment has been efficient. The complications listed are infection in the nail or pin tracts and loosening of the nail or pins. Death of the head may occur, but more frequently replacement of bone by revascularization occurs. Protection from weight bearing for six months or more is important. After operation the activity of the patient should be restored as quickly as possible, and he should be put in a chair in about one week. No weight bearing by the injured leg should be permitted until the trabeculae of the bone are firmly reestablished and this is demonstrated in roentgenograms.

Gissane, Blair and Rank²⁸⁶ present 4 cases of fracture of the neck of the femur which resulted from convulsive therapy administered to patients with mental disorders. The average age was 41. However, attention is called to the fact that extracapsular fractures and intracapsular fractures of the neck of the femur most commonly occur in the aged and feeble. The 4 patients whose cases are presented had all been consigned to institutions for prolonged treatment before convulsive therapy was administered. The authors conclude that the bones have become atrophic from disuse and consequently are liable to fracture if undue strain is placed on them.

284. Treatment of Fractures of the Neck of the Femur by Internal Fixation, Report of the Fracture Committee of the American Academy of Orthopaedic Surgeons, *J. Bone & Joint Surg.* **23**:386-390 (April) 1941.

285. Speed, K.: Symposium on Surgery of Aged: Management of Fractures of Neck of Femur by Operative Fixation, *S. Clin. North America* **20**:75-96 (Feb.) 1940.

286. Gissane, W.; Blair, D., and Rank, B. K.: Fractures of Neck of Femur in Convulsion Therapy, *Lancet* **1**:450-453 (March 9) 1940.

The conclusions drawn from the authors' experiences and a review of the literature are:

1. Convulsive therapy should not be used for elderly persons or for those who have had a prolonged period of inactivity.
2. The minimal number of injections should be used.
3. After the treatment, a routine examination of the skeletal system is indicated.

4. Once the fracture has been diagnosed, the usual treatment should be given.

5. After adequate nailing, there is no reason to withhold further convulsive therapy, if this is still indicated. [ED. NOTE: One of us (H. E. C.) agrees with the authors. However, in 1 of his cases in which there was bilateral fracture of the neck of the femurs following such therapy, the patient was 40 years old and had good bone structure, which was in no way atrophic.]

Harris²⁸⁷ presents 2 cases, in each of which a Smith-Petersen nail was so firmly fixed in the cortex of the femoral shaft that as the neck shortened the nail penetrated the acetabulum. The nail had not been extruded as usually happens with shortening of the femoral neck. In 1 case the fixation was difficult to explain, but in the other case it was due to callus over the head of the nail. In both cases the symptom of painful motion of the hip resulted from the perforation of the femoral head. This complication in the use of the three-flanged nail contraindicates the use of such fixation of the head of the nail to the femoral shaft, advocated by several surgeons. [ED. NOTE: The conclusions by Harris do not bear out the observations of the Fracture and Traumatic Committee of the American Academy of Orthopaedic Surgeons²⁸⁴ on the treatment of fractures of the neck of the femur by internal fixation. This committee found that not only the Smith-Petersen nail but also the Moore nail and other types of fixative material intruded into the acetabulum in 5 per cent of 572 cases; there was extrusion in 8 per cent.]

Christopher²⁸⁸ presents 5 cases of impacted fracture of the neck of the femur in which treatment by means of a short abduction spica, elevation of the heel of the shoe on the normal side and early walking resulted in union and complete recovery. This treatment was a modification of the method of Apfelbach and Aries,²⁸⁹ who reported 22 cases

287. Harris, H. W.: Intrusion of Smith-Petersen Nail into Acetabulum. *J. Bone & Joint Surg.* **22**:999-1003 (Oct.) 1940.

288. Christopher, F.: Treatment of Impacted Fracture of Neck of Femur. *J. Bone & Joint Surg.* **22**:161-167 (Jan.) 1940.

289. Apfelbach, G. L., and Aries, L. J.: Ambulatory Treatment of Fractures of the Neck of the Femur, *Surg., Gynec. & Obst.* **63**:341-348 (Sept.) 1936.

of complete fracture of the neck of the femur with good results in 17. The so-called impacted fracture practically always calls for the same treatment as other fractures of the neck of the femur. [ED. NOTE: It has been the experience of one of us (H. E. C.) that if the general condition of the patient permits impacted fractures of the neck of the femur should be treated as any displaced fracture of the neck of the femur, that is by nailing. How can one always tell how complete and stable the impaction of fractures is?]

Wilson²⁹⁰ reports a series of 10 cases of fracture of the neck of the femur in children observed over a ten year period. A close study of this series forces him to conclude that such fractures are serious injuries and are not always followed by good functional results as most authors report; that maintenance of reduction in the Whitman cast is difficult; that while a nail would perhaps be more effective, there is a possibility that it will damage the epiphysial plate. Changes with growth are to be expected. The disturbances of growth in patients of this series do not conform to the classic picture of Legg-Calvé-Perthes disease. Oblique subtrochanteric osteotomy is helpful in bringing a limited arc of motion into useful planes. In this series there were 7 boys and 3 girls; 4 were in the first and 6 in the second decade of life. One of the children died. The case of another is too recent to report. In 2 of the remaining 8 there were good functional results. [ED. NOTE: This is an excellent and reliable report of results in treating a type of fracture which has not been considered seriously enough in the past.]

Trochanteric Fractures of the Femur.—Leydig and Brooks²⁹¹ report that there is a high mortality rate among patients with trochanteric fractures of the femur. In a series of 302 cases at the St. Louis City Hospital the rate was 39.3 per cent. A survey of seven of the larger private hospitals in St. Louis revealed a mortality of 25 per cent in 335 cases. This is in contrast to the mortality of about 14 per cent implied by the literature and textbooks. The fractures occurred at the average age of 70. If patients withstand the initial shock of injury, they apparently do not well tolerate the treatment, which to be adequate ordinarily requires prolonged immobilization in bed.

Since excellent results were obtained with Smith-Petersen nails, in cases of fracture of the neck of the femur, it was thought that this treatment could be used for fractures of the trochanters. It was used in a series of cases, but apparently the nails did not adequately immobil-

290. Wilson, J. C.: Fractures of Neck of Femur in Childhood, *J. Bone & Joint Surg.* **22**:531-546 (July) 1940.

291. Leydig, S. M., and Brooks, T. P.: Treatment of Pertrochanteric Fracture of Femur with Lag Bolt, *J. Missouri M. A.* **37**:354-357 (Aug.) 1940.

ize the fractures, as in every case there resulted coxa vara and shortening of various degrees.

The mechanics of immobilization by internal fixation in fracture through the neck of the femur and in trochanteric fractures are entirely different. There is a greater shearing action in the latter. For this reason a lag bolt similar to the lag screw of Henderson was devised, which in the opinion of the authors is simple. The patient is prepared with morphine and scopolamine, and the site of the fracture is infiltrated with procaine hydrochloride. The fracture is reduced by traction and abduction. A roentgenogram is taken, and if the reduction is satisfactory an incision is made $1\frac{1}{4}$ inches (3.2 cm.) below the greater trochanter. A $\frac{7}{32}$ inch (0.56 cm.) drill hole is started in the correct direction, and anteroposterior and lateral roentgenograms are taken. If the position is faulty, the direction should be changed. The lag bolt is fitted into a brace and screwed into the drill hole. A wedge-shaped washer is applied, and the prongs of the washer are tamped into the cortex. The washer serves two purposes, namely, preventing rotation of the bolt and diffusing the pressure of the nut over a larger area of the cortex of the shaft. The nut is tightened over the washer, and the wound is closed. The authors have found this method of internal fixation of trochanteric fractures satisfactory. [ED. NOTE: In the past few years much interest has been manifested in the treatment of trochanteric fractures. The high mortality rate in the cases of the authors has not been experienced by many other investigators. However, certain surgeons have had a relatively high mortality rate. Theoretically, internal fixation is ideal for such fractures; however, in using internal fixation surgical shock is to be seriously considered. The authors' technic seems to give less shock and be more ideal than similar methods.]

Fractures of the Shaft of the Femur.—Le Mesurier²⁹² treats fracture of the femoral shaft in children over the age of 2 by placing the leg in a Thomas splint and having the patient lie on an inclined Bradford frame. The tilt of the frame regulates the amount of extension obtained. The end of the Thomas splint is tied on the top of the end rail of the bed so that it cannot rotate. The inclination of the frame should be about one in three; if the frame is 6 feet (182 cm.) long, the inclination should be 2 feet (60 cm.) higher than the head. After about four weeks, when roentgen examination shows callus, a cast is applied. For patients under the age of 2, Le Mesurier uses vertical suspension. He points out that union generally occurs rapidly in children's fractures. [ED. NOTE: One of us (H. E. C.) has had good results in treating fractures of the femur in children up to the age of

292. Le Mesurier, A. B.: Treatment of Fractures of Shaft of Femur in Children, *Am. J. Surg.* 49:140-146 (July) 1940.

5 or 6 years with over head extension. The author's technic for older children is good. However, there is not much difference between his treatment and the well known and long-practiced extension position used in treating fracture of the femur in adults, except that the author does not use skeletal traction. Skeletal traction is seldom desirable or indicated for treating fractures in children.]

Van Gorder ²⁹³ reports 58 cases of fracture of the shaft of the femur. The patients were adults and were treated by skeletal traction. After a careful analysis the following facts are presented: The average stay of the patient in the hospital was eleven and a half weeks. There were 3 cases in which there was nonunion. Of a total of 41 cases 13, or 31 per cent, in which the length of the leg was measured showed an average shortening of $\frac{7}{8}$ inch (2.2 cm.). Motion of the knee joint was limited in 11 of 43 cases, or 25 per cent, with an average limitation of the total range of 76.5 degrees. The average time that elapsed between the date of injury and the date when the patient resumed work was seven and one fourth months. The end results of treating the 58 patients were excellent in 57 per cent, good in 30 per cent and poor in 8 per cent. [ED. NOTE: When properly used the open method of treating fractures of the shaft of the femur necessitates a shorter period of hospitalization, but this report shows that treatment by the closed traction method also gives good results. It takes capable surgeons to use either method, and good supervision and training are demanded by either procedure. No one method is applicable to every case; a decision regarding each case should be made separately.]

In a discussion of fracture of the femur Voshell and Verda ²⁹⁴ present their experiences with the Anderson method of automatic ambulatory treatment. Reduction is accomplished by inserting two pins at a fixed angle to each other into the proximal fragment near the trochanter and two straight pins through the distal fragment near the knee. With the patient lying on the fluoroscopic table in a special traction apparatus which attaches to the pins, the fracture is reduced. A short strong cast is then applied from the groin and buttocks to the knee joint, incorporating both the proximal and the distal pins. The average stay of these patients in the hospital was nine and a half days. In all, 22 patients were treated. Two deaths occurred from bronchopneumonia; both the patients were old people. In 6 cases union was not yet accomplished after three months, but union was ultimately effected in all without surgical intervention.

293. Van Gorder, G. W.: Treatment of Fractures of Shaft of Femur by Skeletal Traction and Thomas Splint, *Am. J. Surg.* 49:149-154 (July) 1940.

294. Voshell, A. F., and Verda, D. J.: Fractures of Femur Treated by Automatic Ambulatory Method of Roger Anderson, *Am. J. Surg.* 49:175-176 (July) 1940.

Injuries of the Knee.—Anderson²⁹⁵ reports a case of fracture of the tibial spine. A satisfactory result was obtained by fixation of the leg in extension in a plaster cast. Fracture of the tibial spine and an avulsion fracture of the tibial attachment of the anterior crucial ligament he states are distinctly separate conditions and should be differentiated. In anatomic dissections of 16 knee joints he found that the anterior crucial ligament was firmly attached to the anterior intercondyloid fossa of the tibia. [ED. NOTE: This is a good article and worthy of more careful study.]

Leadbetter and Hand²⁹⁶ describe the mechanism of fracture of the tibial plateau and discuss the technic of open reduction of the fracture. This paper is based on a study of 23 cases; in 16, or 70 per cent, the fracture was treated by open reduction. Removal of a meniscus was necessary in 12 of these; some form of internal fixation was necessary in 4. In 9, or 56 per cent, a good functional result was obtained; extension was complete, and flexion was beyond a right angle. In 1 case there was moderate genu valgum with good function. In 2 cases fair functional results were obtained, but the postoperative period of convalescence is as yet too short to evaluate the results. Of 7 patients treated by closed reduction, 2 had normally functioning knees, and 3 had limited motion, instability and pain. Two others did not return for study. In the procedure advocated by the authors the damaged soft structures are removed, good contour is restored to the lateral tibial plateau at its weight-bearing surface, and spongy subchondral bone is packed and compressed underneath the plateau for support. Many disconcerting disabilities may be prevented with this procedure. [ED. NOTE: This is a serious fracture, and it demands close and careful treatment. An after-treatment precaution is prolonged freedom from weight bearing.]

Barr²⁹⁷ states that in a series of cases of fracture of the upper part of the tibia, fracture of the outer condyle without associated fracture of the fibula was the type present in 40 per cent and that this is the most common type encountered. For purposes of treatment Barr classifies the cases according to the displacement of the fractured fragments: slight, moderate or marked. This type of fracture assumes a fairly constant form, in which there is a comminuted depression of the central portion of the articular surface of the lateral condyle and a lateral displacement of a large marginal fragment. Manipulation is futile; treatment consists of open reduction and fixation. [ED. NOTE: All patients

295. Anderson, E. R.: Fracture of Spine of Tibia (Intercondyloid Eminence). *Minnesota Med.* **23**:674-677 (Sept.) 1940.

296. Leadbetter, G. W., and Hand, F. W.: Fractures of Tibial Plateau. *J. Bone & Joint Surg.* **22**:559-568 (July) 1940.

297. Barr, J. S.: Treatment of Fractures of External Tibial Condyle (Barr's Fractures), *J. A. M. A.* **115**:1683-1687 (Nov. 16) 1940.

with fractures of this type do not demand treatment by open reduction. One of us (H. E. C.) has treated several patients with fracture of this type by the closed method. However, this does not mean that surgical intervention is never indicated. It is required in cases in which there is marked displacement.]

Macklin, Hartman and Peterson²⁹⁸ report 2 cases of dislocation of the head of the fibula and review the literature on the subject. The diagnosis is made from the history of the onset of pain localized to the region of the head of the fibula and aggravated by motion of the knee joint. The head of the fibula is tender to palpation. There is less pain with the knee flexed. Anteroposterior and lateral roentgenograms show the displacement clearly, but the diagnosis may be missed if one has no previous knowledge of the condition. In a few cases the condition becomes chronic and the patient complains of weakness in the leg. The dislocation usually occurs after a fall on the inverted foot or on the leg doubled up under the body, but it may also be caused by a direct blow or, more rarely, by the pulling action of the muscles. Reduction is accomplished by manual pressure with the knee in flexion to relax spasm of the biceps. Fixation for four to six weeks is recommended. [ED. NOTE: Reduction and maintenance of the position with such an injury is not always as simple as the authors would lead one to believe. However, even with deformity and malposition, functional results are frequently surprisingly good. The authors have outlined an excellent procedure for the treatment of this disability. Open operations are seldom indicated, but one of us (H. E. C.) knows of 1 case in which the surgeon removed the upper end of the fibula with good functional results. Such surgical intervention is not to be carried out except for chronic painful conditions which are not amenable to other treatment.]

Fractures of the Shafts of the Tibia and Fibula.—Swart²⁹⁹ presents a series of 68 cases of fractures of the shafts of the tibia and fibula treated by the Anderson splint. The number of cases of infection, nonunion and slow union is presented, with reasons for these results. The advantages of the method are: The method is positive and certain for early reduction and fixation; the fragments do not slip in the cast; the period and expense of hospitalization are minimized; the patient can walk with crutches at an early date; practically no pain is present after reduction. The disadvantages of the method are: The possibility of infection of the bones is always present; if overpull is not corrected, slow union or non-

298. Macklin, W. E.; Hartman, C. M., and Peterson, H. O.: Dislocation of Head of Fibula: Report of Two Cases, *Minnesota Med.* **23**:649-650 (Sept.) 1940.

299. Swart, H. A.: Analysis of Treatment of Sixty-Eight Cases of Fractures of Shafts of Tibia and Fibula with Roger Anderson Splint, *South. M. J.* **33**:1081-1085 (Oct.) 1940.

union may be the result; rather elaborate equipment is necessary; walking irons cannot be used.

The end results were known in 43, or 63 per cent, of the cases; 39 of these or 90 per cent, were good, and 4, or 9.3 per cent, were poor. Seven, or 10.3 per cent, are still under observation, and the results in 16, or 23.5 per cent, are not known. [ED. NOTE: This is an excellent summary, and the conclusions are reliable. No treatment is infallible or panacean. There must be no forgetting the dangers or making indiscreet use of this or similar technics.]

Nelson and Jenson³⁰⁰ discuss a most important complicated fracture, namely, the "trimalleolar" fracture of the ankle. This was first described by Cooper over a century ago. The term "trimalleolar" is used as a convenience to include the posterior lip of the tibia as a "posterior malleolus." Of 359 cases of fractured ankles, over a period of five years, 77 "minimal" and 10 "classical" trimalleolar fractures were treated. Eight of the 10 cases of "classical" fracture were followed up. From their experience with these cases the authors draw the following conclusions:

1. "Minimal" trimalleolar fracture is a trimalleolar in which the posterior tibial fragment comprises less than one-third of the anteroposterior measurement of the distal articular surface of the tibia. It can in every case be adequately reduced by manipulation under anesthesia with the knee flexed to 90 degrees, and reduction maintained by a plaster cast from the toes to the knee with the foot flexed to a right angle and in mid-position as regards inversion and eversion.

2. "Classical" trimalleolar fracture is a trimalleolar in which the posterior tibial fragment comprises one-third or more of the anteroposterior measurement of the distal articular surface of the tibia. It can be reduced by manipulation, but the reduction can not be maintained in every case, even if the cast extends from the toes to the groin with the knee held in 90 degrees flexion. Therefore, it should be opened, preferably within the first few hours when the skin is still in good condition and swelling absent or minimal. We use Speed's incision—just to the medial margin of the tendo Achillis and vitallium screws to fix the posterior fragment in place. A light dressing is applied, the ankle manipulated to reduce the fractures of the medial and lateral malleoli, and the leg is placed in plaster exactly as for the minimal fractures.

3. In some cases of "classical" trimalleolar fracture, three directional traction in a plaster cast will obtain and maintain reduction; but, because this is uncertain, we believe that it is better to operate immediately. Repeated manipulations, manual or combined with skeletal traction, traumatize the skin and by so doing very frequently preclude any open surgery.

Fracture of the Os Calcis.—Dieterle³⁰¹ reports 1 case in which a man aged 50 had a so-called "open beak" fracture of the os calcis. Open

300. Nelson, M. C., and Jenson, N. K.: Treatment of Trimalleolar Fractures of Ankle, Surg., Gynec. & Obst. **71**:509-514 (Oct.) 1940.

301. Dieterle, J. O.: Case of So-Called "Open-Beak" Fracture of Os Calcis. J. Bone & Joint Surg. **22**:740 (July) 1940.

reduction was necessary because initial reduction had been delayed on account of ecchymosis and swelling. Good results were obtained.

Dieterle states:

This fracture is quite rare and, as stated by Böhler, presents no difficulty in reduction. The tubercle of the os calcis is not pulled upward by the Achilles tendon, but is split off and held in the position as shown by impingement of the sharp edge of the fragment against the Achilles tendon. With the foot in the plantar-flexed position, reduction by manipulation should be easy, provided there are no complications such as occurred in the case reported.

[ED. NOTE: In our opinion this rare fracture is not as easy to reduce by the closed method as Böhler and Dieterle seem to think; open reduction would seem to be indicated in most cases.]

Injuries of the Spine.—Sinberg and Burman³⁰² state that the treatment of fractures of the atlas, whether of the lateral, the anterior or the posterior arch, is the same as the treatment of fractures elsewhere in the cervical region of the spine. The patient's neck is hyperextended in bed by traction, and a plaster jacket of the Calot type is applied when the acute stage is over. This jacket is worn until healing occurs. At this time the neck is supported by a brace and physical therapy is given. The total duration of treatment is as for any injury in the cervical region of the spine, about seven to ten months. Two cases of fracture of the posterior arch of the atlas with associated fractures of the cervical region of the spine at the other points are presented. According to the authors, this association seems to be the rule in such cases. [ED. NOTE: Great care should be exercised to make certain that the spinal cord is not injured before applying traction in treating injuries in the cervical portion of the spine.]

Wilson, Michele and Jacobson³⁰³ state that spontaneous dislocation of the atlantoaxial articulation is a dislocation occurring without known trauma or discernible organic disease of the bone. The authors report 1 case of their own, in which there was complicating quadriplegia, and cite 28 other cases from the literature. They found the incidence equal in the two sexes. The majority of patients were between 5 and 12 years of age; the youngest was 2, and the oldest, 62. The authors' case with the complication of quadriplegia was the only one in which there was involvement of the spinal cord. They observed that dislocation is preceded by infection, most often in the nose and the throat, and that head traction is the best method of reduction and should be followed by use

302. Sinberg, S. E., and Burman, M. S.: Fracture of Posterior Arch of Atlas, *J. A. M. A.* **114**:1996-1998 (May 18) 1940.

303. Wilson, M. J.; Michele, A. A., and Jacobson, E. W.: Spontaneous Dislocation of Atlanto-Axial Articulation, Including Report of Case with Quadriplegia, *J. Bone & Joint Surg.* **22**:698-707 (July) 1940.

of a Thomas collar. [ED. NOTE: Prolonged rest in bed followed by substantial ambulatory fixation is important in these cases.]

Hanflig and Schlosberg³⁰⁴ present a case of spontaneous dislocation of the atlantoaxial joint. They emphasize the fact that atlantoaxial dislocation must be thought of in the examination of any torticollis that occurs in a patient who also has infection in the cervical region of the spinal cord or in the vicinity.

It is important to note that long delay in making the diagnosis does not render a satisfactory reduction impossible. In this case dislocation had existed for almost ten months before it was satisfactorily reduced, and then this was accomplished by manipulation. The reduction has persisted for three and a half years.

Hall³⁰⁵ presents 13 cases with histories and roentgenograms of fractures of the lower cervical and upper thoracic spinous processes. The term "clay shoveler's fracture" is applied to this fracture as it usually occurs in laborers while throwing up a shovel of clay. The clay sticks to the shovel; the worker then feels a stabbing pain and sometimes hears a crack between the shoulders and is unable to continue working. The site of fracture is most commonly the spinous process of the seventh cervical vertebra, but it ranges from the sixth cervical to the third thoracic vertebra. One symptom is pain between the shoulders, nearly always on one side of the midline and capable of being made worse by stretching the arm. The pain may go to the head down the spine or even down the arm. Pain and tenderness and motility at the site of the fracture are present. The treatment indicated is early removal of the detached fragments. [ED. NOTE: This is an interesting and unusual fracture. One of us (H. E. C.) recently had such a case, in which the fracture had been unrecognized by the attending physician and diagnosed as sprain of the neck. It is our experience that this fracture is healed by rest with strapping or other means of support and does not require surgical intervention.]

Eastwood and Jefferson³⁰⁶ state that the common causes of injury to cervical vertebrae are motorcar accidents, diving into shallow water and falling down stairs. Clinically, the cervical portion of the spine can be divided into the first two vertebrae and the last five.

Injuries in the atlantoaxial section of the spine are of two main types: injuries of the odontoid process and dislocations of the atlanto-

304. Hanflig, S. S., and Schlosberg, C.: Nontraumatic Dislocation of Atlanto-Axial Joint, *New England J. Med.* **223**:713-716 (Oct. 31) 1940.

305. Hall, R. D. M.: Clay-Shoveler's Fracture, *J. Bone & Joint Surg.* **22**: 63-75 (Jan.) 1940.

306. Eastwood, W. J., and Jefferson, G.: Discussion on Fractures and Dislocation of Cervical Vertebrae, *Proc. Roy. Soc. Med.* **33**:651-660 (Aug.) 1940.

axial joint. Injuries of the odontoid process may be divided into three classes: fracture of the odontoid process without displacement, fracture of the odontoid process with displacement of the atlas on the axis and displacement forward of the atlas without fracture of the odontoid process.

Diagnosis of fracture of the odontoid process without displacement rests mainly on roentgen examination; treatment consists of complete rest with the neck supported in neutral position in bed by a hard pillow or sandbag supplanted in two or four weeks by a well molded leather collar.

If death does not occur, reduction of fracture of the odontoid process with displacement of the atlas on the axis is usually easily effected through recumbency with some hyperextension. No manipulative treatment or traction on the head is necessary. Reduction should be followed by recumbency for six weeks, and then a carefully fitted leather doll's collar extending from the occiput well down the thorax should be applied. Bony union usually takes place within six months after the injury.

Displacement forward of the atlas without fracture of the odontoid process is usually fatal, as the transverse ligament is ruptured without damage to the bone. For those few patients who survive, treatment differs in no way from that of fracture of the odontoid process with displacement forward of the atlas.

According to Greeley,³⁰⁷ rotary dislocation of the atlantoaxial joint is a rare injury; but reduction is easily obtained with the patient under general anesthesia, and after three weeks' immobilization free use of the cervical part of the spine is permitted. Eastwood and Jefferson obtained good results by treating a 17 year old youth by recumbency for ten days with gentle traction.

Injuries of the lower five cervical vertebrae are usually divided into three types: fracture, dislocation and fracture-dislocation.

When a diagnosis of fracture is made, it is usual to give treatment in hyperextension if the injury is a compression fracture of one of the bodies and in a neutral position if the injury consists of a fracture of the neural arch without displacement.

According to Langworthy, dislocation may be bilateral or unilateral, and symptoms referable to the spinal cord are entirely absent with unilateral dislocation. The mortality rate of bilateral dislocation is high; symptoms referable to the spinal cord are present in 50 per cent of the cases. There are two methods of treatment: immediate reduction with the patient under general anesthesia and slow, gradual replacement by

³⁰⁷ Greeley, cited by Eastwood and Jefferson.³⁰⁶

traction. After reduction there may be recurrence unless immobilization is maintained for at least two months.

Fracture-dislocation has the highest percentage of symptoms referable to the spinal cord and the highest mortality. The commonest sites are the fifth, sixth and seventh cervical vertebrae. Complete dislocation of the articular process does not occur as a rule, and replacement can be obtained by gradually increasing hyperextension. If dislocation is complete, traction is essential before reduction can be obtained. [Ed. NOTE: This is an excellent general outline of the diagnosis and the treatment of these serious injuries.]

Conwell³⁰⁸ states that more than 50 per cent of all fractures of the vertebrae are compression fractures. This percentage is higher for fractures caused by automobile accidents. More than 70 per cent of these fractures occur at the dorsolumbar junction. Of the 13,000 fractured spines in 1937, approximately 8,000 were caused by motor vehicles. One symptom is backache of varying severity; but there may be no visible deformity and the patient may be able to walk. Conwell advises the taking of oblique roentgenograms in certain cases as well as lateral and anteroposterior views.

For corrections the author uses a modified Herzmark frame for hyperextension and places the full convexity of the frame opposite the injury. Gradual production of hyperextension is brought about until at the end of fifteen or twenty minutes full correction is obtained as evidenced by lateral roentgenograms. The patient is kept on the frame for four to six weeks, and then a snug-fitting body cast is applied. Hyperextension is still maintained for five or six weeks more. If roentgenograms show that union and a satisfactory position are developing, a Taylor back brace is substituted until complete restoration of the crushed vertebra is accomplished. Contraindications of this treatment are definite fracture or fracture-dislocation in the posterior arc and separation of the anterior common ligament from the anterior part of the body of the vertebrae. The author has observed paralytic ileus and renal calculi as complications of compression fractures of the spine.

Parnall³⁰⁹ suggests a method of reduction and fixation of compression fractures of the spine that is a simple, inexpensive and convenient means of producing hyperextension. Two strips of spring steel 1 inch (2.5 cm.) wide and 30 inches (76 cm.) long are placed on both sides of the spinal column; a wide metal band is slid under the point of injury and suspended above by a block and tackle. Sand bags are placed under

308. Conwell, H. E.: *Compression Fractures of Spine*, Mississippi Doctor 18:183-189 (Sept.) 1940.

309. Parnall, E.: *Simple Method of Reduction and Fixation of Compression Fractures of Spine*, J. Bone & Joint Surg. 22:1072-1074 (Oct.) 1940.

the shoulders and buttocks to steady the patient. The cast can be applied in the usual manner, and the strips are easily slipped out. Contraindication for this treatment is a fracture of the posterior arc at the point of fulcrum desired. [ED. NOTE: The complication of ileus following the application of a body cast for any vertebral fracture or fractures, especially when it is necessary to bring about rather marked hyperextension, should always be kept in mind. Grave results will occur in some cases if the cast is not immediately removed. When ileus does occur, relief is usually obtained by turning the patient over on his abdomen and using routine surgical procedures.]

Furst³¹⁰ attempts to evaluate the probable significance of the mechanical factors in the production of fractures of the vertebrae after the administration of metrazol therapy. He points out that the anatomic nature of the thoracic region of the spine may explain the frequency of fractures of the fifth, sixth and seventh thoracic vertebrae and that the convexity of the thoracic region is increased by the intervertebral disks, which in this region are slightly narrower in front. Since the mobility in this region is limited to 90 degrees of flexion and only 40 degrees of extension, the flexor muscles of the spine have a definite mechanical advantage over the extensor muscles. It was demonstrated in the laboratory by direct measurement that the periphery of the superior and inferior ventral margins of the fifth thoracic vertebra is crushed by a force about one third of that required to crush the body. It is further pointed out that the compression load placed on a vertebra in the tonic phase of convulsion seems of less importance than the recurrent impacts of the clonic-tonic-clonic convulsion. Furst likewise concludes that compression of the intervertebral disks may follow fracture of the thoracic vertebral bodies in 86 per cent of the cases. Invasion of the prolapsed nucleus pulposus of the disk into the spongiosa of the body of the vertebra, resulting in the formation of a Schmorl node, has been observed. The necessity of maintaining spinal hyperextension in preventing postmetrazol vertebral fractures and intervertebral disk complications after the administration of metrazol therapy is emphasized. Its use may result in reduction of fractures from 50 to 8 per cent. [ED. NOTE: This complication following the administration of metrazol therapy is too common, and the author's suggestions are timely and important.]

Friedman, Brett and Vogt³¹¹ found that roentgenograms of the dorsal and lumbar regions of the spine of 65 institutionalized patients

310. Furst, W.: Force Required to Crush Vertebrae: Its Probable Mechanical Relation to Postmetrazol Fracture, *Psychiatric Quart.* **14**:397-402 (April) 1940.

311. Friedman, E.; Brett, A. L., and Vogt, E. C.: Compressions of Vertebral Bodies During Convulsive Therapy: Preliminary Note Regarding Their Prevention, *New England J. Med.* **222**:704-710 (April 25) 1940.

with chronic psychosis undergoing convulsive treatment showed single or multiple compressions of the vertebral bodies in 11. None of the patients with vertebral compressions had any localized complaints. Neurologic and physical examinations revealed no abnormalities.

No relation was found to exist between the number and severity of the convulsions and the incidence of compressed vertebral bodies. With 1 exception all patients were of the inactive sedentary type. There were predisposing factors in the form of kyphoses, ruptured disks and old compressions of the vertebral bodies in 4 of 13 control cases. Osteoporosis from disuse might also have been an important factor. Precipitating factors were caused by the convulsive procedures themselves. These consisted of sudden flexor activities of the muscles of the trunk, which predominated over simultaneous extensor movements. The already fixed flexed posture of the dorsal region of the spine accentuated by the sag of the bed during treatment seemed to bring about a convergence of the acting muscle forces on the arched portion of the dorsal region of the spine, where all the compression injuries were found. Employing the knee support of a standard surgical bed as an adjustable vertebral hyperextension frame prevented compression injuries of the vertebrae in 16 consecutive cases.

Compound Fractures.—Orr³¹² states that for any method of treatment of compound fractures to be effectual it must not neglect the absolutely essential fundamentals of immediate reduction of the fracture, drainage of infected wounds, immobilization in correct position and control during repair of the fracture. Restoration of the circulation and nerve supply and provision for rest to favor physiologic function in injured and inflamed parts must not be neglected as they were in the World War. He recalls a program which he proposed in 1923; it consists of the following measures:

1. Relieve the shock and reduce the fracture immediately by adequate traction.
2. Institute complete débridement and drainage. (He advises use of iodine and alcohol to swab out the wound.)
3. Use nonabsorbent, nonirritating petrolatum packing to fill the wound; this protects the surface and allows permanent drainage.
4. Enclose the entire limb in a plaster of paris cast with whatever fixation is necessary.
5. Wait until the patient's condition warrants the removal of the severely injured limb if indicated; pain and shock, however, should be relieved beforehand.
6. Finally, do no postoperative dressings.

312. Orr, H. W.: Treatment of Compound Fractures, with Special Reference to Military Surgical Procedures, Arch. Surg. 40:825-837 (May) 1940

He then points out six misconceptions which must be laid aside if such a program is to be followed. The experience of the author and of other competent observers who employed these principles in more than 10,000 cases in the Spanish civil war shows that good results may be obtained by the infrequent dressing method with 85 to 90 per cent of compound infected fractures of all kinds. [ED. NOTE: No one treatment is applicable to all compound fractures in military and civilian life. Orr has, however, presented some excellent principles to be used in certain compound fractures (infected) occurring under certain conditions.]

Trueta and Barnes³¹³ point out that hitherto the efforts of surgeons in the treatment of infected wounds have mainly been directed toward destroying bacteria by the use of antiseptics. Far too little attention has been paid to the natural powers of the tissue to localize and kill bacteria. Application to the wounds of an antiseptic that will kill bacteria will damage the tissue and disturb the injured parts.

The method of treating infected wounds in a closed plaster cast is based on entirely different principles and appears to offer a solution to the problem. The essential points are cleansing the wound with soap and water, performing thorough débridement, insuring adequate drainage by opening up all deeper tissues and completely immobilizing all soft tissue by enclosing the injured part in a plaster cast. The healthy tissue underneath presents an absolute barrier to the entry of bacteria into the general circulation.

For freshly infected wounds they advocate thorough excision of all dead tissue and complete immobilization of all soft tissue not only of the joints but of the entire limb. This prevents the flow of lymph and minimizes the absorption of bacteria from the site of the wound. With wounds that have been present for twelve hours or more, complete immobilization of the inflamed wound will reduce the chances of bacteria passing out of the inflamed area into the circulation. The closed plaster technic is employed for wounds in the process of healing. The wound is left undisturbed for days or even weeks at a time; thus the granulation tissue can act as an effective barrier to infection. [ED. NOTE: One of us (H. E. C.) disapproves the authors' technic for treating fresh wounds. Here again a thorough débridement with mechanical cleansing and the application of sulfanilamide with immediate closure of the wound without a plaster cast are in most instances the most favorable treatment.]

313. Trueta, J., and Barnes, J. M.: Rationale of Complete Immobilization in Treatment of Infected Wounds, *Brit. M. J.* 2:46-48 (July 13) 1940.

Baillat³¹⁴ describes his experiences with the treatment of fractures by immobilization in occlusive plaster casts in the recent Spanish civil war and states the method is known as the "Spanish method." He writes that Trueta in a hospital in Barcelona found it satisfactory where supervision and primary surgical treatment had been adequate. The treatment consists of reduction by an extension apparatus and immobilization in a plaster cast. The first plaster cast was left in place for ten to fifteen days and the second for twenty to thirty days; the third was left in place for one month. Infected tissue was usually not left in the fracture area; if it was, the plaster cast was opened to insure drainage. Amputation was necessary in only 1 of 615 cases. Functional results were usually satisfactory. Pseudarthrosis developed in 3 cases because of excessive loss of tissue. Stiffness of the joints, especially in the knee or elbow, resulted in a few cases. There were only 2 cases of complete ankylosis.

Baillat has used this method in his ordinary practice as well as in the treatment of war wounds in the Spanish civil war. The results after appropriate operation were good in the majority of cases. He is convinced of its definite value in the treatment of war wounds. [Ed. NOTE: It is difficult to truly evaluate the final results of this treatment in view of the type of warfare which has been and is being carried on in the European countries. Under war conditions, which in most instances were and are chaotic, this treatment is probably efficient in many cases and most of the time is the only way out. It is, however, difficult to see how this treatment is superior to other methods of treatment and should be advocated when more favorable surroundings and a well trained staff with the proper equipment are available, whether the situation occurs in regular practice or under war conditions.]

During the Spanish civil war, d'Harcourt, Folch Pi and Oriol Angeura³¹⁵ were personally responsible for the treatment of 7,500 fractures, and they followed up 17,000 patients treated in other centers. As a result of their experience, they extended the closed plaster method of treating fractures to the treatment of injuries of soft tissues in cases in which there was much loss of substance. The method was used both at an early stage (within six or eight hours after the infliction of the wound) and at a later stage, when the wound had already begun to granulate. Only slight variation in technic was required for the two types. The technic permits a great deal of conservative treatment. In

314. Baillat, G.: *Therapy of War Fractures by Occlusive Plaster Apparatus*. Rev. d'orthop. 26:656-663, 1940.

315. d'Harcourt, J.; Folch Pi, A., and Oriol Angeura, A.: *Closed Plaster Method of Treatment: Account of Its Use During Spanish War*, Brit. M. J. 1:652-654 (April 20) 1940.

the battle of the Ebro a surgical unit dealt with 120 casualties, and in only 5 cases were amputations necessary. At the Vallcarca Hospital in Barcelona, 5,000 wounded were treated in one year (the wounds were fractures almost exclusively); secondary amputations were performed on only 26 of these, and few serious complications were encountered. There were 20 cases of gas gangrene; in 12 of these there were vascular lesions. The number of deaths among the 5,000 patients was 27; of these 15 were due to gas gangrene, 17 to septicemia and 5 to secondary hemorrhage. There were no instances of nonunion or malunion from faulty position of the fragments, although in a number of comminuted fractures many broken pieces of bone had lost all nutrient connection.

In a few cases nonunion occurred in the forearm, the result of extensive loss of substance. Osteomyelitis complicating fractures was not serious, but it was persistent. The closed method of treatment did not have any definite detrimental or beneficial effect on this complication. The method reduces the period of healing, particularly that of the preliminary state of disintegration. The strict immobilization of the wound insures a faster growth of epithelium and prevents the distribution and absorption of products of disintegration which would occur with constant handling. The method does not interfere with the natural process of healing, which would be disturbed by the application of antiseptics. Proteolysis does not occur. Dehydration due to evaporation at the surface of large wounds is considerably reduced, and this in itself is an important factor in the healing of the wound and the restoration of the patient's health.

Key and Burford³¹⁶ point out the great decrease in the incidence of infection after the implantation of sulfanilamide in compound injuries and emphasize that the wound must also be débrided and cleansed in the usual manner. They performed a series of experiments to determine whether sulfanilamide inhibits the healing of bone. They fractured one bone of each foreleg in a group of rabbits, implanted sulfanilamide on one side and left the other side as a control. In one group of dogs, the ulnas were fractured, and all dogs received sulfanilamide by mouth. In a second group of dogs the ulnas were fractured, and sulfanilamide was not administered. All wounds healed by primary intention, and the sites of fracture were examined microscopically and roentgenologically at intervals. No difference in the degree and rate of bony union was discovered in any group. [ED. NOTE: This report of Key and Burford presents reliable information and a valuable contribution

316. Key, J. A., and Burford, T. H.: Local Implantation of Sulfanilamide in Compound Fractures: Its Effect on Healing, *South. M. J.* **33**:449-455 (May) 1940.

on the use of sulfanilamide in fractures and wounds of the soft structures. Too much emphasis cannot be placed on this adjunct treatment to the true and tried mechanical cleansing and débridement of the wound and compound fracture.]

Cannaday³¹⁷ presents the following advantages of primary closure of compound fractures:

1. The period of hospitalization is shorter.
2. After healing, the injured limb is left in a much better condition. If the treatment is successful, the limb is covered with relatively normal skin rather than with a large area of scar tissue of low vitality.
3. The loss of time and the expense of care can be kept down to a reasonable minimum. However, the technic can be carried out successfully only by a surgeon thoroughly trained in this class of work. It requires a most scrupulous asepsis and meticulous attention to detail. The author performs a careful débridement with irrigation of the wound with warm saline solution. Primary closure is done with the aid of relaxing lateral incisions when necessary. The author does not favor the use of internal fixation for compound fractures. [Ed. NOTE: This paper emphasizes a technic which should not be neglected, even when sulfanilamide is used. The author's main ideas have been espoused by many others for the last quarter of a century or more. No surgeon can expect that his patient will be 100 per cent free from infection. However, in view of the inevitable percentage of infection in using the author's technic, what objection could there be to using sulfanilamide to try to reduce infection? Internal fixation is indicated in certain compound fractures, and when indicated, it should be used.]

Reynolds, Zeiss and Cubbins³¹⁸ state that the specific aim of their report is to investigate the incidence of wound infection in compound fractures in two groups of patients. One group was treated by sharp débridement, followed if necessary by cleansing the interior of the wound with copious floodings of bland solutions, such as saline solution or soft soap U. S. P. followed by saline solution. For the second group practically the same routine was utilized, but iodine and alcohol were introduced into the depths of the wound after débridement. A study of 131 consecutive cases of compound fracture was made. The authors emphasize that no 2 cases were alike in extent of injury or amount of contamination and that there was also a difference in the general condition of the patients. The large percentage of deaths (31) is accounted

317. Cannaday, J. E.: Primary Closure of Traumatic Wounds with Especial Reference to Conversion of Compound into Simple Fractures, *Am. J. Surg.* **47**:375-390 (Feb.) 1940.

318. Reynolds, J. T.; Zeiss, C. R., and Cubbins, W. R.: Compound Fractures, *Arch. Surg.* **40**:844-852 (May) 1940.

for by the poor general condition of the patients when admitted. An analysis of 88 cases is presented, in half of which the wounds were flooded with iodine and alcohol before cleansing and in the other half of which only a bland solution followed by saline solution was used. Infection developed in 18.1 per cent of the patients treated with iodine and alcohol and in 13.1 per cent of the others. The greater number of infected wounds in those cases in which iodine and alcohol were used is explained on the assumption that the iodine causes death of a sufficiently large number of cells to allow infection to take place. [Ed. Note: This is another demonstration that débridement and mechanical cleansing of the wounds are more important than the saturation of a wound with antiseptics. This statement, however, is not in condemnation of the use of sulfanilamide after proper mechanical cleansing and débridement of a wound or compound fracture.]

McKee³¹⁹ outlines a quick and simple method of treating compound fractures of the leg by the use of a special apparatus he employs. McKee feels that his technic will prove of value when large numbers of compound fractures have to be dealt with at the same time. The apparatus consists essentially of clamps by which Steinmann pins can be fixed to the side bars of a Thomas splint. Details of the treatment are given, and the after-treatment is described. The method is quick, easy, safe and effective. It is eminently suitable for immobilizing compound fractures of the leg under war conditions.

Multiple Fractures.—Hudson³²⁰ reports 30 cases of multiple fractures involving two or three extremities which were accompanied by fractures of the pelvis, the spine, the ribs, the skull or the face but were not complicated by intra-abdominal lesions.

Hudson uses the following method of treating these patients: The patient who is in shock of some degree varying from moderately severe to extremely severe is immediately given a hypodermic injection of a mixture of $\frac{1}{400}$ grain (0.0006 Gm.) of scopolamine, $\frac{1}{4}$ grain (0.015 Gm.) of morphine sulfate and cactin. No inhalation anesthesia is used or needed. Although the procedure may be painless with only this mixture, the additional measure of infiltration with procaine hydrochloride may make it completely so. Hudson uses this medication in all cases of trauma requiring early operation. Patients with fractures of the skull may be treated by this procedure. The patient is placed in the shock position. An intravenous injection of 1,500 cc. of 5 per cent dextrose in saline solution is given. Roentgen examinations are then made with a portable

319. McKee, G. K.: Treatment of Compound Fractures of Leg, *Lancet* 2:38-40 (July 13) 1940.

320. Hudson, O. C.: Multiple Fractures, *J. Bone & Joint Surg.* 22:354-360 (April) 1940.

machine. The extremities are shaved without removing the temporary immobilization. One hour is allowed for the maximum effect of the hypodermic injection to take place. Treatment is instituted by a trained team, compound lesions are débrided, and fractures are then reduced and immobilized with their permanent fixation dressing. The patient is returned to bed and the foot of the bed elevated. A transfusion is given.

Immobilization is maintained until complete osseous healing has occurred. Active muscle exercises of all nonimmobilized joints and of all immobilized extremities are done hourly from the day of injury until the patient is discharged. The tendon sense is maintained, and stiffness and atrophy of the joint are prevented. The mortality rate is rather high. Hudson treats every patient that is not moribund on admission as if he would recover. The condition of the patient who dies within one to twelve hours after admission is usually hopeless from the beginning. Since adopting this method of treatment, Hudson has found that the patient was more comfortable owing to complete immobilization of the fractures; the shock was less, and the recovery from shock was shortened to between twelve and twenty-four hours. The end results were better anatomically and functionally. [ED. NOTE: It is gratifying to note the increasing interest being manifested in the early care of the injured. Surgeons should learn to perfect themselves in this care before expecting the public to know what to do. It behooves surgeons, however, to make the public conscious of certain elementary procedures in caring for those injured by accidents and thereby to prevent many unnecessary disabilities and, in many instances, even death.]

Skeletal Traction.—Mathewson³²¹ states that skeletal traction, long considered feasible by surgeons, had to await the introduction of aseptic surgery for its safe and full application. He points out the complications which may arise in the wake of enthusiasm for all types of skeletal traction from the misuse rather than the application of the method. The greatest danger is infection, which may result from the use of improper technic at the time of application or from the subsequent motion of the metal agent used for traction. The latter is particularly apt to lead to infection if the direction of motion is along the axis of insertion. This will not occur at first, as the nail or pin is embedded in the bone. Later, as traction is applied, aseptic pressure necrosis takes place, and the nail becomes loose. To prevent this the author uses metal sleeves (even these are not infallible) to fit over the skeletal traction wires (rather than Steinmann pins). These sleeves are placed firmly against the cortex of bone on either side and extend to the

321. Mathewson, C., Jr.: Misuse of Skeletal Traction, *Am. J. Surg.* 47: 408-430 (Feb.) 1940.

spreader or stirrup. The same result can be obtained by incorporating the traction wires in a plaster cast.

The complications of infection are most severe when a hematoma, a joint or an unrecognized linear fracture communicating with a major fracture is traversed by a traction pin. Improperly placed pins may result in inefficient traction, pressure necrosis of soft tissues or severe damage to the bone or neighboring epiphysal areas of a joint. The use of metal tongs is condemned, except for traction on the skull in fractures of the cervical part of the spine.

Aside from infection, distraction is the greatest danger associated with skeletal traction, leading to delayed union or nonunion. Too much weight over too long a period not only will cause distraction, but will stretch the musculature so that it loses its power to contract. Although distraction does occur in single point traction, its possibility is greatly increased when multiple sites of traction are used.

The ambulatory management of patients treated by the incorporation of the skeletal pins in plaster of paris casts is considered dangerous, particularly when weight bearing on the skeletal pins is allowed. [Ed. Note: This is an excellent and timely discussion.]

X. FRACTURE DEFORMITIES

Physiologic Factors in the Healing of Fractures.—The physiologic factors concerned with the healing of fractures and the formation of callus have been the subject of much experimental and clinical study in recent years. The p_H of the fluids in the tissues near the site of the fracture has been compared to that of the blood serum, and any definite changes have been noted. Achlorhydria has been observed as a depressing influence, or at least a frequent accompaniment of delayed union in fractures.

Tollman, Drummond, McIntyre and Bisgard³²² conducted an experimental study of tissue metabolism and phosphatase activity in early formation of callus. Adult rabbits in which experimental fractures of the radius had been produced by osteotomy were used. Blood was removed before and after death for determination of the phosphatase content. After three or four days callus was removed for the study of metabolic activity. It was observed that there was a general falling off in metabolic activity as the age of the callus increased; the authors felt this was due to decreased activity of the tissue. Calcification showed a general increase with age of the callus, but there was variability. On microscopic examination specimens with a high calcium content showed

322. Tollman, J. P.; Drummond, D. H.; McIntyre, A. R., and Bisgard, J. D.: Tissue Metabolism and Phosphatase Activity in Early Callus. Arch. Surg. 40:43-48 (Jan.) 1940.

the best developed bone, with formation of well defined spicules. The phosphatase activity was relatively low at the start but rose with active proliferation of bone. There was a close correlation between the amount of calcification and the amount of phosphatase activity. The authors found that the degree of healing in the early stages was dependent not so much on the age of the fracture as on the amount of phosphatase produced. This was shown in 1 rabbit which became infected and was killed on the seventh day. The phosphatase activity was about one-tenth that observed in another rabbit which was uninfected and was killed the same day. The amount of calcification was also less.

No definite shifts in the values for blood phosphatase were observed. There was an initial rise in tissue metabolism of the callus, followed by a fall. There was an irregular increase in phosphatase activity and calcium deposition with time. The changes in concentration of serum phosphatase were not characteristic. A close relation was found between the phosphatase activity of the callus and the amount of calcium deposition.

Pollock,³²³ impressed by the frequency of central fractures of the neck of the femur and atrophic spondylitis in elderly women as compared with men in the same age groups, thought there might be some relation between this fracture and the cessation of ovarian function.

In searching for experimental confirmation of his impression that estrogen influenced calcification, a study was made of the production of callus and healing of bone in a series of experimental fractures in rats. Normal adult female rats, adult female rats spayed at three months for other experimental work and young female rats spayed just before the present experiment were used. After experimental fractures had been produced, large doses of estrone (theelin) were given to two groups and withheld from the others. The following observations were made after operation:

In group A, or that which corresponded to healthy, nonspayed rats, callus was present in 2 of the 4 survivors (50 per cent) by the end of the third week following fracture. In group B, in which the rats had been spayed, no callus was found at the end of twenty-one days, whereas in group C, in which the animals were spayed and then treated by huge doses of theelin, calcification was present in 50 per cent by the fourteenth postoperative day and in 75 per cent by the twenty-first postoperative day at its lowest estimation.

In the younger age groups, confirmatory findings were obtained. In group E in which theelin was not given, callus was not present by the end of the fourteenth day. By the end of the twenty-first postoperative day, callus was present in one with a faint possibility of some being present in a second rat. In group D in which theelin was given, 50 per cent showed the presence of callus by the end of the fourteenth postoperative day and 75 per cent by the end of the twenty-first day after operation.

323. Pollock, G. A.: Effect of Theelin on Fracture Repair, *Proc. Staff Meet. Mayo Clin.* 15:209-214 (April 3) 1940.

Pollock concludes that the results which followed the administration of estrone were sufficiently striking to indicate that ovarian secretory influences calcification and in cases of fracture may accelerate solid union.

[ED. NOTE: This interesting piece of experimental work probably has little practical therapeutic value at present. While the cessation of the depression of ovarian function apparently is a contributing cause of senile osteoporosis, dysfunction of the entire endocrine system is involved in the problem. Many patients with senile osteoporosis and delayed unions in fractures have been treated with large doses of estrone over prolonged periods, but no increase in calcification has been demonstrated roentgenologically and no acceleration in union of the fracture has been noted.]

Calcification in the Soft Tissues Adjacent to Fractures.—The deposition of calcium in hematomas, muscles, ligaments and tendons adjacent to fractures or associated with simple traumatic injuries of joints is a well recognized condition. The physiologic or pathologic processes producing such deposition have not yet been satisfactorily explained. The amount of soft tissue injured or the extent of the hematoma does not have any influence. Brumbaugh³²⁴ discusses the problem and reports 3 cases of calcification resulting from injury to tendinous and ligamentous tissue of the elbow, the knee and the shoulder. The exact process by which traumatized tendon fibers calcify and often later ossify has not been clearly demonstrated, and the author does not add to the knowledge. He states that Callen's³²⁵ conclusion regarding Pellegrini-Stieda disease is justified, namely, that this particular condition is not a disease entity but represents a local manifestation in the knee of post-traumatic changes common to other joints. He believes that the processes in the three joints, as illustrated by his cases, are identical.

Atrophy of Bone.—One of the distressing aftermaths of the treatment of fractures may be excessive atrophy of the bone. Jordan³²⁶ emphasizes some measures in the after-care of fractures which can prevent this. He stresses the importance of instituting physical therapy immediately after reduction and immobilization. He states that overstretching is often an important and overlooked cause of atrophy of muscle. In determining the best position for immobilization, the effect of that position on all the muscles acting on all the joints of the extremity is to be considered. The author believes that mechanical factors play a

324. Brumbaugh, H. L.: Calcifying Tendinitis Traumatica: Diagnosis and Treatment of Post-Traumatic Changes In and About Joints, *Am. J. Surg.* **48**:681-684 (June) 1940.

325. Callen, H. S.: Pellegrini-Stieda's Disease: Manifestation in Knee of Post-Traumatic Changes Common to Other Joints, *Radiology* **29**:158-165 (Aug.) 1937.

326. Jordan, H. H.: After-Care of Fractures with Special Reference to Delayed Union and Sudeck's Atrophy, *Arch. Phys. Therapy* **21**:25-32 (Jan.) 1940.

dominant role in nonunion. Frequently, the union is not actually delayed but the period of immobilization is too short. To overcome the fear of prolonged immobilization, he emphasizes that stiffness of a normal joint will not occur from fixation in a normal position no matter how long continued, especially if the whole extremity is immobilized. Complicating the after-care of the fracture may be an acute atrophy of bone (the so-called Sudeck atrophy). Although Sudeck now believes this condition to be a physiologic reaction to trauma, Jordan points out that the typical mottled appearance in the roentgenogram is accompanied by pain and disability, which require treatment. He believes that weight bearing and exercises in unpadded plaster casts are the most effective form of treatment.

Ghormley³²⁷ discusses post-traumatic painful atrophy of joints and distinguishes this as a clinical entity from Sudeck's atrophy and from atrophy of disuse. The usual picture is that of a sprained ankle or knee relieved by rest and immobilization; the patient then resumes activities, and gradually pain and swelling appear in the affected joint; the patient then finds relief again in immobilization, but again experiences difficulty with renewed activity. Thus a vicious circle is set up. Treatment is based on gradually increasing and constant exercise. Massage, at first light and then heavier, is used and followed by carefully planned active exercise. The latter is the most important phase. Weight bearing is begun with crutches after confidence is acquired. By this regimen normal activity is usually established in three months, but complete restoration to normal may require several more months. The author believes that sympathectomy is not indicated, because all patients will recover with properly supervised conservative measures. Supplements of calcium and vitamin D to the diet are worth while.

[ED. NOTE: Jordan and Ghormley's articles, although presenting little new, emphasize important factors in the treatment and prevention of an unlooked for complication which might result in permanent disability.]

Correction by Growth of Deformities Resulting from Fractures in Childhood.—The general principle that subsequent changes with growth will correct even gross deformities due to malunion of fractures occurring in childhood must be accepted with reservations. Stimson,³²⁸ after analyzing a group of such deformities, lays down fundamental principles to be used as guides in determining whether or not to correct certain deformities resulting from fractures in childhood.

327. Ghormley, R. K.: Post-Traumatic Painful Atrophy of Joints. *Arch. Ped. Therapy* 20:725-731 (Dec.) 1939.

328. Stimson, B. B.: Growth Correction of Deformities Resulting from Fractures in Children, *S. Clin. North America* 20:589-592 (April) 1949.

First, the younger the child the better the eventual correction will be. Fractures occurring during delivery, especially in the shafts of long bones, heal remarkably well and gross displacements correct themselves over a relatively short period of time. Large masses of callus are quickly formed about the ends of the fragments, and even though the ends of the bones are widely displaced, a new shaft will be fashioned from this mass of callus as it condenses. This assumes the contour, the alinement and usually the approximate length of the normal shaft. Any deficiencies in length are made up by compensatory overgrowth. Splinting, sufficient to immobilize temporarily and maintain approximate alinement, is all that is required.

A second fundamental principle is that growth will tend to correct the displacement in complete transverse fractures of the long bones if the axes are maintained. The author feels that "operative interference in these cases is not justified unless there is interposition of soft structures or evidence of severe circulatory or nerve damage." [Ed. NOTE: Circulatory or nerve damage rarely occurs in children in connection with fractures, except supracondylar fractures at the elbow. In most instances manipulative correction of the gross deformity at the site of fracture is also sufficient to care for circulatory or nerve complications. Early operative interference in threatened or established Volkmann's ischemic paralysis has been advocated in articles by several other authors; the practical value of such procedures appears doubtful. The indications for the necessity of the operation are indefinite and difficult to determine in the early stage. In most cases a decision based on the initial symptoms would subject the patient to an unnecessary operation and complicate the treatment of the fracture. On the other hand, if the decision to operate is delayed until the condition is evident, it is too late to accomplish any material benefit.]

A third fundamental principle is that, in angular deformities, the outline will tend to become rounded out, converting the sharp angle into a curve rather than resulting in a straight bone.

In certain locations this may result in disability. The disability appears to depend on two factors: the direction of the bowing and the site of the fracture. This is best shown in fractures of the forearm. Dorsal bowing resulting from fractures in which the distal fragment is tilted volarward interferes with rotation less frequently than volar bowing. Fractures in the middle portions of the shafts permitted to heal with deformity are more likely to result in disability than those in the lower third. Fractures of the lower end of the radius united with either dorsal or volar angulation often show little, if any, correction from compensatory growth. When this deformity exists to an appreciable extent, particularly in connection with dorsal angulation, it may produce disability and should be corrected.

The question of compensatory overgrowth in the shaft of the femur after fracture in children has been carefully analyzed by Aitken.³²⁹ He presents a study of the end results in 71 cases of fracture of the femoral shaft in children under 16 years of age. The patients have been followed

³²⁹. Aitken, A. P.: Overgrowth of Femoral Shaft Following Fracture in Children, *Am. J. Surg.* 49:147-148 (July) 1940.

from three months to eight years and are divided into two age groups: one 13 years of age or older and the other 12 years of age or younger. In the older age group are 6 patients with an average period of five years since fracture. All fractures either were anatomically reduced or had lateral displacement without shortening. In 5 cases an average shortening of 1 cm. is present. One patient, 13 years of age at the time of the fracture, has a lengthening of 1.6 cm.; the epiphyses are closed, so the lengthening is permanent. In the group 12 years of age or younger there are 65 patients. In this group all but 1 show lengthening of the femur from the position on discharge. In 9 patients anatomic reduction was obtained. In 1 there is no difference in length, while in 8 the fractured femur averages 1.1 cm. longer. Seven patients were discharged with lateral displacement but no shortening; these show an average lengthening of 1.1 cm. One patient, whose limb was overpulled by 0.7 cm., now has lengthening of 1.7 cm. In 8, open reductions were performed, and anatomic position was maintained in 4; in these, the femurs are now 1 cm. longer. In 4, bowing occurred, shortening the femur an average of 0.8 cm.; these have an average lengthening of 0.8 cm., making an average overgrowth of 1.6 cm. Thirty-eight patients were discharged with complete displacement and overriding. In 21 patients, the fractured femur is longer than the sound one. In 9 patients, the average shortening was 1.2 cm. and the average length is now 0.4 cm., an average overgrowth of 1.6 cm. In 12 patients on discharge, a shortening of 0.6 cm. was present; there is now an average lengthening of 0.7 cm., an overgrowth of 1.3 cm. In 17 patients, there is still some shortening. In 11 patients, the average shortening on discharge was 1.3 cm., and final shortening was still 0.5 cm. In 6 patients the average shortening was 0.6 cm. and is now 0.2 cm. It is noted that the patients showing the most shortening on discharge now show the most overgrowth. The greater the displacement, the larger the callus and the longer it persists.

Overgrowth of 1 cm. occurred in 2 patients with pathologic fractures. In 9 patients with fractures over one year old and in 2 patients with fractures of less than six months' duration, there was overgrowth of 0.3 cm.; in 7 patients with fractures of six months' to one year's duration the average overgrowth was 1 cm. Overgrowth occurs while callus is still present. The type or site of the fracture made no difference. The author believes the overgrowth is due to periosteal stimulation resulting from periosteal hyperemia. He doubts that the overgrowth is balanced by the time of epiphysial closure and cites 9 cases in which it has not occurred.

[ED. NOTE: Fractures and dislocations involving the epiphysis and growth lines may frequently produce disturbances in future growth, and the development of varus or valgus deformities of the adjacent joint.]

shortening of the shaft. The subsequent disturbance in growth does not depend solely on the amount of apparent damage to the epiphysial line. Some patients with simple fracture running transversely across the epiphysial line without displacement will show retardation of growth with deformity. On the other hand, in certain complete epiphysial separations, such as that of the lower end of the radius, which have not been reduced and have united without contact between the epiphyses and the shaft, normal length and alinement of the bone are the usual result.]

Treatment of Malunited and Ununited Fractures.—Fractures of the distal ends of the metacarpal bones, "knuckle fractures," are commonly regarded as trivial injuries, and the treatment given in many instances is inadequate to prevent crippling deformity. When such deformity occurs in the first, second or third metacarpal bone, function in the fingers may be severely impaired for occupations requiring accurate coordination of finger movement.

Although many methods of closed reduction and splinting have been described, the consensus of most surgeons is that none of them are dependable to reduce and maintain the proper position of the fracture. The usual result is a malunion with the head and articular surface of the metacarpal articulation angulated and depressed toward the palm of the hand, with shortening of the metacarpal and limitation of flexion of the finger.

Haboush³³⁰ presents the regional anatomy and pathology of fractures of the knuckle and describes an operation designed to restore the flexor action of the finger.

The metacarpophalangeal joints have no true capsule but are invested by a synovial sac reenforced by the tendons and two collateral ligaments. The space between the synovial sac and the extensor tendon is normally filled with loose areolar tissue. This space is important in that it makes possible a wide excursion of motion of the extensor expansion as it glides over the synovial membrane and smooth dorsal angle of the metacarpal bone. Callus or adhesions in this space limit the excursion of the extensor expansion and prevent complete flexion of the joint.

In a case described by Haboush, one of a malunited fracture of the distal end of the fifth metacarpal bone, the space just described was filled with a dense fibrous tissue resembling fibrocartilage. The extensor tendon expansion was firmly adherent to this mass, impairing flexion of the finger. Removal of this mass of fibrous tissue and of the adjacent callus and projecting edges of the fractured shaft on the ulnar side was carried out, thus diminishing the anterior posterior and lateral diameters

330. Haboush, E. J.: Malunion of Fracture of Head of Metacarpal Bone (Knuckle Fractures): Simple Operation for Correction, *J. Bone & Joint Surg.* 22:1054-1058 (Oct.) 1940.

of the metacarpal bone and establishing a normal relationship with the flexor and extensor tendons.

The author states that six weeks after operation there was normal flexion in the finger.

[ED. NOTE: In this procedure no attempt is made to correct the primary anatomic deformity of the fracture. It seems probable that the palmar angulation and tilting of the articular surface of the metacarpal head must contribute to the dysfunction and that any operation which does not at least partly remedy this anatomic deformity will fail to restore function, at least in the first three metacarpal bones, where functional disturbance is usually greatest.

Experience has shown that correction of malposition after union is difficult in the early stage owing to osteoporosis of the distal fragment. Later, after the bone has recalcified, an osteotomy can be performed to correct the palmar angulation and the shortening. The position is maintained by means of an intramedullary bone peg extending from the shaft into the head; the gap on the palmar surface is filled with a small bone wedge.

A better solution of the whole problem of these fractures would be to assume a more positive attitude in treating them at the time of acute fracture and to do an immediate open reduction and internal fixation with a medullary bone peg. The same conditions pertain to displaced fractures of the metatarsal heads.]

Masland³³¹ describes a splint to be used in the conservative treatment of nonunion in fractures of the bones of the forearm and other long bones. The operation of the splint produces continuous distraction of the bone in its normal alinement with opportunity for both flexion and rotation of the forearm. It proposes to secure by continuous distention what cannot be accomplished by immediate extension of the injured member. No statistics of the number of cases in which the splint has been used or of the end results are given.

[ED. NOTE: A careful distinction between delayed union and true nonunion is essential in estimating the value of any method of treatment. With the conditions of a real nonunion present, bone grafting has proved to be the most reliable and in the end the most conservative method of inducing union.]

Abbott³³² advocates the use of manipulation and skeletal traction in a Thomas splint for the treatment of malunited and ununited fractures of the shaft of the femur. It is his opinion that operation on patients

331. Masland, H. C.: Conservative Treatment of Non-Union, *Am. J. Surg.* 47: 170-171 (Jan.) 1940.

332. Abbott, L. C.: Treatment of Malunited and Ununited Fractures of Shaft of Femur by Manipulation and Skeletal Traction, *Am. J. Surg.* 49:181-182 (1940).

who are seen within a few months after the fracture may be avoided. Simple manipulation with freeing of the fragments in both malunited and ununited fractures, followed by skeletal traction, will often bring about union with correct alinement and full length of the limb. The simplest method of obtaining proper length and alinement without complicated operative procedures is the preferred treatment of these fractures and in the long run will yield the most satisfactory results.

The necessity of maintaining traction until the callus uniting the fracture has completely consolidated is strongly emphasized. Failure to observe this fundamental principle will often result in recurrence of the deformity. The average period of traction required for a malunited fracture of the femoral shaft is about twelve weeks.

The same principle is applied to the treatment of ununited fractures of the shaft of the femur. Manipulation of these fractures serves a twofold purpose: it disengages the fragments from a mass of fibrous tissue and callus, and by so doing it stimulates the callus to renewed activity. Union may be hastened by percussing the callus with a rubber hammer and by placing constricting rubber bands above and below the fracture site, an old method described by Hugh Owen Thomas.

The greatest difficulty encountered in the one stage operative method of treatment is to overcome the shortening of the extremity due to the overlapping of the fragments with accompanying contractions of the soft tissue. Consequently, even though some type of operation is to be employed, manipulation and skeletal traction are valuable preliminary procedures.

Henderson³³³ discusses the entire problem of ununited fractures and analyzes the end results of such fractures treated by bone grafts at the Mayo Clinic up to 1936.

Patients with ununited fractures are usually in excellent general health, and no clue as to cause can be elicited by the most painstaking general examination. The causative factors in nonunion are local and not systemic. Regulation of diet and administration of calcium or of glandular extracts are of no benefit. Physiologic inertia exists at the site of fracture; this must be done away with and the process of bone regeneration initiated if union is to occur. The most dependable method of accomplishing this is the use of autogenous bone grafts.

The experience gained from a study of this large series of bone grafts has crystallized certain cardinal principles regarding the selection of cases, operative technic and after-care; the surgeon should keep them constantly in mind. They are:

1. No ununited fracture should be subjected to direct operative attack if there are any draining sinuses or if there is any latent infection in the vicinity of the fracture.

333. Henderson, M. S.: Problem of Ununited Fracture, *Am. J. Surg.* 47:454-465 (Feb.) 1940.

2. Fibrous tissue should be removed from between and about the bone ends; the medullary cavities should be opened, and the ends of the bones fitted, so that they can be held in close apposition by the aid of a bone graft.

3. The graft must be long and large enough to insure large surface contact of graft with both fragments. The bone graft serves two functions, a physiologic function in stimulating formation of bone and a mechanical function in providing internal fixation.

4. The graft must be held securely to the fragments by aid of beef bone screws, autogenous bone pegs, metal screws or metal bands. Multiple chips of bone should be packed along the line of fracture and as much as possible along the line of contact of the bone graft with the fragments. The more bone that is brought to the site of fracture the better.

5. External fixation, preferably by casts, must be provided for sufficient time to protect the graft during the period of "weakness," which develops about the fourth to the sixth week. This protection is particularly necessary in cases of fracture of the humerus or femur. Three months is the earliest that external fixation can be abandoned and some sort of protection is often essential for six months from the time of operation.

6. It must be constantly kept in mind that repair of bone is always slower to be induced after it once has failed. The second attempt at repair is certain to be slower in starting, developing and finishing than nature's first attempt. Because of that fact careful supervision of resumption of function, as to time, manner and amount, is the definite responsibility of the surgeon.

Henderson reports the relative incidence of ununited fractures of various bones as follows:

In a review of the records of 583 patients with ununited fractures treated by bone grafting operation from 1912 to 1936 inclusive in The Mayo Clinic, the relative incidence as to the bones involved was as follows: tibia, 233 cases; humerus and femur, 100 each; radius alone, seventy; radius and ulna combined, forty-four; ulna alone, thirty; clavicle, five; and metatarsal, one.

The relative results in the treatment of fractures of different bones were:

In 530 cases the end results were definitely determined. The results following bone graft of the tibia were the best in that in 94 per cent of cases the fragments united. Success was obtained in the treatment of fractures of other bones as follows: the radius alone in 93 per cent of cases; the ulna alone in 89 per cent; the humerus in 86 per cent; the radius and ulna in 85 per cent and the femur in 78 per cent. Difficulties encountered in dealing with individual bones differ with the location of the fracture, be it in the upper, middle or lower third.

Le Cocq³³⁴ describes a method of treating ununited fractures, using vitallium plates to secure stability and fragments of bone removed from the ilium to promote osteogenesis. He says the rationale of the method is based on the belief that bone grafts held with autogenous bone pegs loosen after a few weeks and permit motion at the site of fracture.

334. LeCocq, E.: Ununited Fractures of Both Bones of Forearm. *New York Med. J.* 65-166 (May) 1940.

between the graft and the bone before union has occurred, thus increasing the percentage of failures.

[ED. NOTE: Reported statistics of authors using massive onlay grafts record bony union in about 90 per cent of cases; the failures are due chiefly to infection or extensive osteosclerosis of the ends of the fragments but rarely to loosening of the graft. The substitution of metallic screw fixation of the onlay graft, which has been adopted by many surgeons, eliminates the difficulties formerly encountered in obtaining firm fixation of the graft by means of autogenous bone pegs. Physiologically, bone grafts are better osteogenetic agents than plates, which inhibit the production of callus over the area to which they are applied. Failure of union due to fracture of the graft occasionally occurs in locations, such as the upper third of the femur, where there is great mechanical stress. In such locations the metallic plate applied adjacent to the graft or on top of it has been added and this appears to be a more desirable method of obtaining additional fixation than substitution of the plate for the graft.]

Since the earliest use of bone grafting in the treatment of ununited fractures there have been conflicting opinions about the role played by the periosteum in the process of union. Pollock and Henderson³³⁵ in a series of experimental grafts on the femurs of dogs endeavored to throw some further light on this controversial subject. Ten bone grafting operations were carried out. In 5, the periosteum was retained; in 5, it was removed. From analysis of the end results of the experiment the authors conclude that no advantage is gained by retention of the periosteum and that removal of the periosteum results in formation of a more active periosteum from the surrounding connective tissues.

[ED. NOTE: The results of this experiment accord with the clinical data derived from a study of many thousand bone grafts employed in the treatment of ununited fractures in human beings. Most onlay bone grafts are removed without their periosteum. There is no clinical evidence to indicate that the revascularization and incorporation into the host bone of such grafts differ in any way from the assimilation of grafts in which the periosteum is retained. The high percentage of unions obtained with the use of either type (about 90 per cent) indicates that there is no essential difference in their practical application.]

In certain locations, such as the lower jaw, the problem of bone grafting for nonunion is complicated by the possibility of unavoidable infection of the operative wound. Under such conditions the usual massive onlay graft may be lost as a sequestrum before sufficient time has elapsed to effect its revascularization. Pedunculated grafts to which

335. Pollock, G. A., and Henderson, M. S.: Value of Periosteum in Grafting Operation, *Proc. Staff Meet., Mayo Clin.* 15:443-448 (July 10) 1940.

the blood supply has been preserved have proved satisfactory in avoiding this complication.

Cole³³⁶ reports a case of pathologic fracture of the mandible with nonunion due to osteomyelitis of the jaw. The lesion was treated by a pedunculated graft. The fragments were bridged by a portion of bone removed from the lower border of the jaw in front of the site of nonunion. The blood supply of the transplanted bone was maintained by the preservation of the attachment to it of the platysma myoides muscle and the deep fascia. These structures were so freed and fashioned as to permit shifting of the graft in position with perfect ease and without tension on the nutrient tissues.

In the case reported the graft took well. Observation three and a half years later showed no asymmetry of the facial contour, and movement of the tongue was free. Cole does not believe, as some do, that from this type of graft, functional disability caused by restriction of movements of the tongue and of the muscles of the floor of the mouth will result.

[ED. NOTE: This type of graft has been used in several cases by one of us (J. S. S.) with excellent results.]

Disability resulting from fractures about the ankle is due either to malposition or to traumatic arthritis or to a combination of the two. In malunions after the usual Pott's, or bimalleolar, fracture, satisfactory restoration of alinement with preservation of motion in the ankle and good function can usually be obtained. In cases of Cotton's, or trimalleolar, fracture, in which the astragalus has been displaced backward and upward with the posterior malleolus, the results of conservative reconstructions which attempt to retain motion in the ankle have proved disappointing. The operative and manipulative trauma to the articular surfaces of the tibia and astragalus necessary to restore position of the fragments produces disabling traumatic arthritis in such a high percentage of cases that primary fusion of the ankle is the procedure of choice. Persistent disability due to traumatic arthritis of the ankle and/or of associated tarsal joints should be treated by fusion of the affected joints. Hamsa³³⁷ outlines the chief causes of disability from fractures of the ankle and discusses the method of examination to evaluate the disability.

In a certain number of cases, resulting traumatic arthritis may be treated conservatively with surprisingly good functional results. When

336. Cole, P. P.: Pathologic Fracture of Mandible: Non-Union Treated by Pedicle Bone Graft, *Lancet* 1:1044-1045 (June 8) 1940.

337. Hamsa, W. R.: Principles of Reconstruction in Ankle Malunion, *New England M. J.* 25:218-221 (June) 1940.

it does not respond after a reasonable period of conservative effort, an operation should be performed.

The various types of disability are classified, and appropriate surgical treatment is given. For malunion of the tibia and fibula associated with disalignment, Hamsa advises supramalleolar osteotomy and astragalectomy if both the ankle and the subastragalar joint are involved. The foot may be stabilized and alined by arthrodesis of the subastragalar and midtarsal joints if these have been injured. Ununited fragments should be removed unless their absence would decrease the stability of the ankle. Fusion of the ankle joint should be done if this alone is involved, or panastragalar arthrodesis, if all three joints are involved. Fracture of the head of the astragalus, the author believes, should be treated primarily by operative measures, that is, fusion of the astragaloscaphoid joint or, if necessary, a triple arthrodesis. For young persons conservative treatment may be tried. For fracture of the body of the astragalus he favors operative treatment, preferring arthrodesis to astragalectomy. Fracture of Stieda's process indicates surgical removal.

[ED. NOTE: Astragalectomy is undesirable for adults and should be avoided if possible.]

Nonunion of Fractures of the Neck of the Femur.—For nonunion of less than three months' duration, King³³⁸ advises fixation of the fragments by the Smith-Petersen nail and a bone graft, taken either from the fibula or from the tibia. For patients over 60 years of age this operation is preferable to subtrochanteric osteotomy. The patient may be up in two weeks without external immobilization, although weight bearing is not permitted for six to twelve months. If the fracture has been present for more than three months, osteotomy is preferable because changes in the head of the femur are liable to follow osseous union. The author takes issue with those who feel that the use of the Smith-Petersen nail causes aseptic necrosis. He states that aseptic necrosis occurs just as frequently when the Whitman method is used; the degree of necrosis is proportionate to the amount of damage to the circulation at the time of injury.

[ED. NOTE: The method of nailing in fractures of the neck of the femur is now widely recognized as constituting a distinct advance. There is, however, a type of case in which aseptic necrosis of the head of the femur occurs with or without union. In cases of this type the procedure advocated by King has been practiced also by Gallie with good results. One of us (L. C. A.) feels that some consideration should be devoted to the Brackett procedure supplemented by nailing, drilling or bone grafting.]

338. King, T.: The Value of Femoral Osteotomy for Diseases and Injury to the Hip Joint, *M. J. Australia* 1:253-268 (Feb. 24) 1940.

Miltner³³⁹ describes an operation for nonunion of fractures of the neck of the femur with "live" heads. The shaft, neck and inferior surface of the femoral head are exposed through a straight lateral incision. An oblique osteotomy is made through the shaft of the femur at an angle of 45 degrees on a level with the inferior surface of the head. A portion of the inferior surface of the head is removed, and the distal fragment is displaced medially under and into the denuded surface of the head. A plaster cast is applied. This is a modification of the Lorenz procedure, differing in that it is intra-articular and that the femoral head is cut to allow contact with the raw surface of the femoral shaft. The procedure was used successfully by the author in 3 cases only.

[ED. NOTE: This technic and similar ones are becoming more popular and certainly have their place in selected cases. Surgical shock is minimized, and excellent results have been obtained in many cases.]

XI. BONE TUMORS

General Considerations.—For purposes of uniformity and clarity in the discussion of bone tumors, it is desirable that most workers in this field make every effort to use the classification prepared by the Committee of the Registry of Bone Sarcoma of the American College of Surgeons.³⁴⁰ This should serve as the basis of further classification and in time permit the establishment of categories for some of the unusual bone tumors now reported individually.

Ludford³⁴¹ has studied the interaction in vitro of fibroblasts and sarcoma cells with leukocytes and macrophages. He reports a series of experiments in vitro which confirms Carrel's demonstration that cultures of leukocytes produce substances which stimulate the growth of fibroblasts and sarcoma cells. He observed that fibroblasts or sarcoma cells when grown together with cultures of leukocytes produce earlier and more extensive growth than when grown alone. Stimulation of growth occurs without actual contact. When they are grown in contact with cells from cultures of leukocytes, not only is their growth stimulated but their capacity for proteolysis is increased. In mixed cultures both kinds of cells remain in a more active functional state. This study of the interaction of these cells in vitro leads the author to suggest that macrophages and monocytes by stimulating growth and proteolytic

339. Miltner, L. J.: Operation for Ununited Fracture of Neck of Femur, *J. Iowa M. Soc.* **30**:9-11 (Jan.) 1940.

340. Ewing, J.: Review of the Classification of Bone Tumors, *Bull. Am. Coll. Surgeons* **24**:290-295 (Sept.) 1939.

341. Ludford, R. J.: Interaction in Vitro of Fibroblasts and Sarcoma Cells with Leukocytes and Macrophages, *Brit. M. J.* **1**:201-205 (Feb. 10) 1940.

activity of malignant cells facilitate the invasive growth of these into normal tissues *in vivo*.

In a study of 28 cases of bone tumor by Cade, Maclagen and Townsend,³⁴² determinations of serum phosphatase were made. The results support the hypothesis that the level of the enzyme in the blood serum reflects the degree of osteoblastic activity in the bones, assuming that the possibility of gross hepatic damage has been excluded. They regard the estimation of serum phosphatase as of some value in following the treatment of osteogenic sarcoma and in detecting the onset of metastases in these conditions. Determination of serum phosphatase can sometimes indicate the presence in the bones of late metastases from other organs, such as occur with carcinoma of the prostate gland, and the test is suggested as a routine procedure in treating this condition. The method of determination used was that of King and Armstrong.³⁴³

Hansen, Ziegler and McQuarrie³⁴⁴ followed carefully the disturbance of osseous and lipid metabolism in a child with primary carcinoma of the liver. The patient was a 10 year old boy with a tumor mass in his liver, marked hyperlipemia and marked demineralization of all bones. The autopsy revealed a hepatoma with considerable destruction of the liver. In studies of metabolism over a period of two years, the authors demonstrated: marked hyperlipemia, explained on the basis of faulty function of the liver; impaired retention of calcium and phosphorus, showing a deficiency of these substances; deficiency of vitamin D (the possibility of hyperparathyroidism and destruction of bone by tumor or infection having been excluded). The calcium phosphate and calcium carbonate ratio increased. There was a definite analogy to the deficiency of calcium. The tentative conclusion is that the liver plays an essential role in osseous metabolism by means of an unknown substance.

Weber³⁴⁵ states that erythroblastemia due to both destruction and irritation of the hemopoietic tissue often accompanies secondary neoplastic infiltration of the bone marrow. The blood counts show nucleated red blood cells in the circulating blood in newborn children with congenital syphilis, in von Jaksch's anemia, in fetal erythroblastosis, in Cooley's anemia, in excessive erythropoiesis from various causes, in Addison's anemia, in Lederer's anemia and in hemolytic jaundice. Erythroblastemia is valuable in differentiating secondary neoplastic

342. Cade, S.; Maclagen, N. F., and Townsend, R. F.: Serum Phosphatase in Cases of Bone Tumor, *Lancet* 1:1074-1075 (June 15) 1940.

343. King, E. J., and Armstrong, A. R.: Convenient Method for Determining Serum and Bile Phosphatase Activity, *Canad. M. A. J.* 31:376-381 (Oct.) 1934.

344. Hansen, A. E.; Ziegler, M. R., and McQuarrie, I.: Disturbance of Osseous and Lipid Metabolism in Child with Primary Carcinoma of Liver, *J. Pediat.* 17:9-30 (July) 1940.

345. Weber, F. P.: Erythroblastemia and Its Value in Diagnosis of Neoplastic Infiltration of Bone Marrow, *Lancet* 1:1077-1078 (June 15) 1940.

infiltration of bone marrow and so-called osteitis condensans ilii. In the author's opinion, osteogenic sarcoma does not lead to erythroblastemia.

Osteomas.—Schwartz³⁴⁶ reviews 48 cases of osteoma of the cranium from the standpoint of roentgenology. He classifies the tumors according to anatomic location: 60 per cent were in the frontoethmoidal regions, 13 per cent in the orbitoethmoidal region and 13 per cent in the parietal region. Osteoma is usually exostotic but may be enostotic. While recognizing that the cause is unknown, Schwartz feels that growth may be stimulated by trauma. The greater the density of the tumor, the more slowly it grows.

Schwartz³⁴⁷ likewise reports a series of 5 cases of osteofibroma of the cranium. The first symptoms were local tenderness and tumefaction, and in 2 cases there was a definite history of trauma in the area involved. He describes the difficulty of differentiating this tumor from hyperparathyroidism, meningioma, metastatic tumors, osteomyelitis (especially syphilitic), cavernous hemangioma and localized lesions of the early stage of Paget's disease. He recommends surgical treatment, because the results of roentgen therapy are disappointing.

Giant Cell Tumor.—In a study of giant cell tumor of bone, Jaffe, Lichtenstein and Portis³⁴⁸ present a concept which can be briefly summarized as follows: The giant cell tumor of bone is not as common or as miscellaneous a lesion as has been generally supposed. Medullary fibroma or osteofibroma, medullary xanthofibroma or xanthogranuloma and certain peculiar forms of medullary chondroma, for instance, are sometimes misclassified under the head of giant cell tumor, notably as representing supposed variants of the latter. They deprecate this tendency and feel that the resemblance between the "brown tumor" of hyperparathyroidism and certain epulides, on the one hand, and the genuine giant cell tumor, on the other, is only superficial. They conceive the giant cell tumor as a neoplasm of a definite kind, arising from the undifferentiated supporting connective tissue of the marrow and composed of a more or less vascularized network of spindle-shaped or ovoid stromal cells and multinuclear giant cells. There is little collagenous differentiation and almost no evidence of ossification. They have classified giant cell tumors into three grades. They also show that a typical giant cell tumor is not likely to develop in a person below 20 years of age. There is no characteristic roentgen picture of this tumor, and they

346. Schwartz, C. W.: Cranial Osteomas from Roentgenologic Viewpoint, *Am. J. Roentgenol.* **44**:188-196 (Aug.) 1940.

347. Schwartz, C. W.: Osteofibroma of Cranium from Roentgenologic Viewpoint, *Am. J. Roentgenol.* **43**:53-57 (Jan.) 1940.

348. Jaffe, H. L.; Lichtenstein, L., and Portis, R. B.: Giant Cell Tumor of Bone: Its Pathologic Appearance, Grading, Supposed Variants and Treatment, *Arch. Path.* **30**:993-1031 (Nov.) 1940.

feel that a biopsy should always be done to establish the diagnosis and that "blind" irradiation based on an unverified roentgen diagnosis alone is not justifiable. They recommend that treatment be based on the grade of aggressiveness and the location of the individual lesion.

A giant cell tumor of the patella is reported by Richards, Giberson and King.³⁴⁹ They have collected 16 previously reported cases of giant cell tumor of the patella. The diagnosis in their case was confirmed by microscopic study; the tumor was removed by curettage and the cavity packed with bone chips. The immediate result is reported to be excellent.

A giant cell tumor of the jaw, subperiosteal in type, is reported by Potts.³⁵⁰ He finds no previous report in the literature of a subperiosteal giant cell tumor of the skull or of the jaw. Geschickter and Copeland³⁵¹ cited 22 cases of giant cell tumor of the skull or of the jaw; in all these cases the tumor arose from those portions of bone which were preformed in cartilage. They predicted that since the periosteum has osteoclastic activity, any giant cell tumor arising from bone preformed in membrane should be subperiosteal; their prediction is fulfilled in Potts's case.

Malignant changes in giant cell tumors of bone are discussed by Fell³⁵² in the report of 3 cases. In 2 of these there were definitely malignant changes; in the other case the tumor is still under observation. In the first case the tumor was definitely malignant five and a half years after curettement. The original tumor was in the distal third of the femur. There was evidence of metastatic sarcoma in the inguinal glands. Death occurred two months after amputation. The second case, after two curettements at ten month intervals, showed a picture typical of osteogenic sarcoma. The lesion was in the distal third of the radius. The patient was still alive at the time of writing, five months after disarticulation at the shoulder.

Osteogenic Sarcoma.—In a study on the morphogenesis of extra-skeletal osteogenic sarcoma and pseudo-osteosarcoma, Binkley and Stewart³⁵³ describe a number of tumors of soft tissue having an epithelial origin but resembling osteogenic sarcoma. From their attempts to discover morphologic changes to explain this resemblance, they conclude that the assumption of the structure of osteogenic sarcoma is the result

349. Richards, V.; Giberson, A. F., and King, D.: Giant Cell Tumors of Patella, *West. J. Surg.* **48**:47-49 (Jan.) 1940.

350. Potts, W. J.: Subperiosteal Giant Cell Tumor, *J. Bone & Joint Surg.* **22**:417-420 (April) 1940.

351. Geschickter, C. F., and Copeland, M. M.: Tumors of Bone, revised ed., New York, American Journal of Cancer, 1936.

352. Fell, E. H.: Malignant Giant-Cell Tumors of Bone, *Internat. Clin.* **2**:199-205 (June) 1940.

353. Binkley, J. S., and Stewart, F. W.: Morphogenesis of Extra Skeletal Osteogenic Sarcoma and Pseudo-Osteosarcoma, *Arch. Path.* **29**:42-56 (Jan.) 1940.

of the laying down of dense hyaline tissue, probably resulting in ischemia, and of the development of a cavernous telangiectatic type of circulation favoring stasis and consequent probable anoxemia; that is, osteogenesis is the result of the local condition. Their studies, however, fail to explain the structure of cartilage-containing mixed tumors.

Batts³⁵⁴ reports an osteogenic sarcoma of the thyroid gland in a woman 71 years of age. The tumor had been present for fifty-two years. At the time of examination the basal metabolic rate was + 31 per cent. A subtotal thyroidectomy was done. In the tissues there was a "spindle-celled osteoid-osteo-fibrosarcoma" arising on an old thyroid adenoma. He cites 7 cases previously reported in the literature.

Ewing's Tumor.—Meyerding and Pollock,³⁵⁵ and Clegg and Macey³⁵⁶ discuss the difficulties of the diagnosis of Ewing's tumor, particularly of differentiating it from osteomyelitis. Hamilton,³⁵⁷ in a more general discussion, reports 28 cases of Ewing's tumor. Three of his patients were free of symptoms after five years.

Neely and Rogers³⁵⁸ have written about the roentgenologic and pathologic considerations of Ewing's tumor, contending that it constitutes an intergradation with lymphoblastoma and myeloblastic tumors on the one hand and with fibrosarcoma and osteogenic sarcoma on the other. Their conclusions are:

1. Ewing's tumor represents an arbitrary subdivision of malignant neoplasms of bone. Histologically, it cannot be considered a neoplastic entity.

2. Roentgen signs of Ewing's tumor are not unequivocally characteristic. They result from destructive and reparative processes in osseous tissue, any of which may be seen in osteogenic sarcoma, a metastatic tumor or a non-neoplastic lesion.

3. Correlation of clinical, roentgenologic and histologic data is necessary to establish the correct diagnosis and proper classification of primary bone tumors.

4. Biopsy should be done as early as possible in any case of a lesion of bone suspected of being a primary neoplasm.

354. Batts, M., Jr.: Osteogenic Sarcoma of Thyroid Gland: Report of Case. *Am. J. Surg.* **49**:390-392 (Aug.) 1940.

355. Meyerding, H. W., and Pollock, G. A.: Ewing's Tumor (Hemangio-Endothelioma; Endothelial Myeloma; Solitary Diffuse Endothelioma): Problem in Differential Diagnosis, *Minnesota Med.* **23**:416-423 (June) 1940.

356. Clegg, R., and Macey, H. B.: Differential Diagnosis of Destructive Lesion of Long Bone: Report of Case, *Proc. Staff Meet., Mayo Clin.* **15**:317-319 (May 15) 1940.

357. Hamilton, J. F.: Ewing's Sarcoma (Endothelial Myeloma), *Arch. Surg.* **41**:29-52 (July) 1940.

358. Neely, J. M., and Rogers, F. T.: Roentgenological and Pathological Considerations of Ewing's Tumor, *Am. J. Roentgenol.* **43**:204-210 (Feb.) 1940.

Willis³⁵⁹ discusses metastatic neuroblastoma presenting the Ewing syndrome and Ewing's sarcoma. He has had personal experience with 2 cases of bone tumor in which the diagnosis of Ewing's sarcoma was made on the basis of adolescence of the patients, a fusiform tumor, an onion skin lamination of the bone observed on roentgen examination and radiosensitivity of the tumor. Both these tumors proved to be secondary to neuroblastoma. The author reviews some recent publications on Ewing's tumor and concludes that the subject is chaotic, that the occurrence of a primary growth of bone of this nature is unproved and that metastatic growth of the type described will probably prove responsible in many cases.

Myeloma.—A case report of plasma cell myeloma needs consideration because of its infrequency. King³⁶⁰ reports a solitary plasma cell myeloma of bone which existed for five years in the trochanteric region of the right femur before the onset of symptoms of multiple osseous lesions. Multiple myeloma was the final diagnosis.

A plasma cell myeloma in a child 9 years of age is reported by Gordon and Schneider.³⁶¹ They report the growth as representing one extreme of a series of multiple myelomas; at the other end of this series there was a typical multiple myeloma showing nodular involvement of the bony skeleton. They state that plasma cell myeloma may occur without any of the signs of multiple myeloma and that the diagnosis at this stage depends on the examination of the blood and on the microscopic examination of the sternal marrow.

Plasma cell myeloma of the eleventh thoracic vertebra with intraspinal epidural extension is reported as a Cabot case.³⁶² Laminectomy at the level of the eleventh thoracic vertebra demonstrated a dense tumor in the epidural space. The laminae of the eleventh dorsal vertebra were soft and infiltrated by the tumor, which on microscopic examination proved to be a plasma cell myeloma.

In another Cabot case³⁶³ the autopsy showed multiple lesions of a lymphoblastic myeloma with extensive involvement of the skeletal system and also multiple foci of tumor growth in the cortex of the kidney. In

359. Willis, R. A.: Metastatic Neuroblastoma in Bone Presenting Ewing Syndrome with Discussion of "Ewing's Sarcoma," *Am. J. Path.* **16**:317-332 (May) 1940.

360. King, B. B.: Solitary Plasma Cell Myeloma of Bone as Initial Stage of Multiple Myeloma, *J. A. M. A.* **115**:36-38 (July 6) 1940.

361. Gordon, H., and Schneider, B.: Plasma-Cell Myeloma in Child: Report of Case, *Internat. Clin.* **4**:173-181 (Dec.) 1940.

362. Plasma Cell Myeloma of Eleventh Thoracic Vertebra, with Intraspinal Epidural Extension, Cabot Case 26072, *New England J. Med.* **222**:274-276 (Feb. 15) 1940.

363. Lymphoblastic Lymphoma, Cabot Case 26221, *New England J. Med.* **222**:927-929 (May 30) 1940.

the liver, there was evidence of hemopoiesis, compensatory for the extensive destruction of the marrow.

Hodgkin's Disease.—A case of Albers-Schönberg disease (marble bones) associated with Hodgkin's disease is described by Herscher and Stein.³⁶⁴ They describe the association of Albers-Schönberg disease with fluorine intoxication and believe that in fluorine intoxication the excessive calcification frequently extends into adjacent structures of soft tissues, whereas in Albers-Schönberg disease this does not happen. Well defined differences are shown also in the histologic study. The causative factors in this case are not known, but the parents and the grandparents of the patient show a high incidence of Albers-Schönberg disease, and there is frequent occurrence in more than one member of the family. This suggests a hereditary defect of germ plasma which results in a disturbance of the whole hemopoietic system. Excessive osteoblastic activities involved most or all of the skeleton with association of fibrosis and enlargement of the liver, spleen and lymph nodes. Hemopoiesis is generally depressed.

Chordoma.—The problem of chordoma is reviewed in three papers. This tumor must be considered in a study of bone tumors because of the destruction of bone caused by its growth. The literature contains more than 150 cases. The chordoma arises from remnants of the embryonic notochord. The sacrococcygeal area is the most common site; one half of the tumors reported arise in this region. One third are in the suboccipital region. Roentgenologically the tumor is clearly outlined, with a midline area of bone destruction. It is very vascular and rather soft and translucent. The symptoms and signs arise from local pressure. The Mixters³⁶⁵ report 3 cases and describe the surgical management used in them. Bowers³⁶⁶ and Richards and King³⁶⁷ report single cases and outline their surgical technic. Local recurrence is the rule, and the prognosis is not satisfactory.

Synovioma.—Lewis³⁶⁸ presents 4 cases of synovioma in which there were unusual and similar roentgenographic findings. The diagnosis was synovioma or synovial sarcoma. In 2 of the cases there was clinical evidence that the tumor was malignant. In the other 2, although the growth was regarded as malignant or potentially malignant from the

364. Herscher, H., and Stein, J. J.: Osteopetrosis Associated with Hodgkin's Disease: Review of Literature and Report of Case, *Am. J. Roentgenol.* 43:74-83 (Jan.) 1940.

365. Mixer, C. G., and Mixer, W. J.: Surgical Management of Sacrococcygeal and Vertebral Chordoma, *Arch. Surg.* 41:408-421 (Aug.) 1949.

366. Bowers, W. F.: Sacrococcygeal Chordoma: Case Report, *Nebraska M. J.* 25:341-342 (Sept.) 1940.

367. Richards, V., and King, D.: Chordoma, *Surgery* 8:409-423 (Sept.) 1941.

368. Lewis, R. W.: Roentgen Recognition of Synovioma, *Am. J. Roentgenol.* 44:170-174 (Aug.) 1940.

pathologic viewpoint, it had not shown recurrence or metastasis thirteen and seven months after operation, respectively.

The author summarizes his article as follows:

1. Four cases are described and illustrated in which distinctive and essentially identical roentgenograms were found to indicate malignant, or potentially malignant, synoviomas or synovial sarcomas.

2. This distinctive roentgen finding seems to occur in about 25 per cent of synoviomas.

3. Thus far, no other pathological condition giving similar roentgen findings has been encountered.

4. Whenever roentgenograms similar to those described are encountered, a provisional diagnosis of synovial sarcoma is justified, and the probability of malignancy should be borne in mind.

Black³⁶⁹ reports a case of interdigital tumor of the foot of two years' duration. He states that although the great majority of synovial tumors so far reported have proved to be malignant a relatively benign type of bursal synovioma is believed to exist, as illustrated in this case and one which he previously reported. It is possible that the tumors might ultimately have become malignant if they had not been removed. Both, however, grew slowly and remained encapsulated for long periods (two and three years, respectively) prior to operation.

Stack³⁷⁰ reports a case of synovial granuloma, a pediculate tumor of the knee with recurrent spontaneous hemarthrosis. "Microscopically the mass was found to be granulomatous in nature. Numerous inflammatory cells, fibroblasts and capillary blood vessels of various sizes were the essential features of the picture."

Xanthoma.—In a clinical and pathologic study of xanthoma of tendon sheaths and synovial membranes, Galloway, Broders and Ghormley³⁷¹ review 70 cases and conclude that

Xanthoma of the tendon sheaths and synovial membranes is a benign lesion associated primarily with an alteration in the lipid metabolism secondarily set off by trauma, infection, or both. It is classified under the heading of the primary essential xanthomatoses.

Hemangioma.—The literature on vertebral hemangioma with neurologic symptoms is reviewed by Kelly.³⁷² He summarizes his findings as follows:

369. Black, W. C.: Synovioma (Synovialoma) of Foot: Case, *Am. J. Cancer* 39:199-206 (June) 1940.

370. Stack, J. K.: Spontaneous Hemarthrosis Due to Synovial Granuloma. *J. Bone & Joint Surg.* 22:735-737 (July) 1940.

371. Galloway, J. D. B.; Broders, A. C., and Ghormley, R. K.: Xanthoma of Tendon Sheaths and Synovial Membranes: Clinical and Pathologic Study, *Arch. Surg.* 40:485-538 (March) 1940.

372. Kelly, L. C.: Vertebral Hemangioma with Neurologic Symptoms, *New York State J. Med.* 40:1607-1612 (Nov. 1) 1940.

1. Primary hemangioma of the vertebra is a comparatively common condition but rarely gives rise to symptoms.

2. Symptoms, when present, may be divided into two groups: (a) compression of the spinal cord; and (b) pain in the back, with or without radiation.

3. Diagnosis can safely be made by the characteristic coarse-meshed appearance of the body of the vertebra produced by the vertical striations alternating with large areas of rarefaction in the bone.

4. Surgery should be attempted at once in all cases with advanced neurologic symptoms who are good operative risks, whereas radiation should be tried in those patients in whom pain is the only symptom or who are not in a position to undergo a major surgical procedure.

[ED. NOTE: In the opinion of other observers, roentgen therapy is the treatment of choice.]

Neurilemmoma.—DeSanto and Burgess³⁷³ report 2 cases of neurilemmoma in bone. They state that neurilemmoma is a specific form of nerve sheath tumor which may occasionally occur as a primary tumor of bone and that the probable origin of the growth in the 2 cases cited and in the 2 previously reported in the literature is the nerve sheaths in the cortex or maybe the periosteum. Neurilemmoma may invade and excavate bone by direct extension from a paraosseous focus. Involvement of bone by a neurogenic tumor does not of itself indicate a sarcomatous transformation of a benign tumor. The authors caution that neurilemmoma of bone is not to be confused with neurofibroma.

The treatment suggested is conservative and consists of thorough curettage with cautery or subperiosteal resection and bone grafting. The possibility of neurilemmoma should be considered in diagnosing cystic expansive rarefactions of the midshafts of long bones.

New Types of Bone Tumors.—In 1935, Jaffe³⁷⁴ reported 5 cases of osteoidosteoma. He and Lichtenstein³⁷⁵ now present a second publication on this tumor with special reference to cases in which a lesion in the cortex of the shaft of a bone is commonly misclassified as sclerosing and nonsuppurative osteomyelitis or abscess of the cortex. They report a total of 33 cases with clinical, roentgenologic and histologic discussions as evidence that this condition is a benign neoplasm. They describe the lesion as being always small and affecting a single bone; it may develop in the substantia spongiosa or the cortex, and it stands out from the surrounding bone as a sharply delimited nidus.

373. DeSanto, D. A., and Burgess, E.: Primary and Secondary Neurilemmoma of Bone, *Surg., Gynec. & Obst.* **71**:454-461 (Oct.) 1940.

374. Jaffe, H. L.: "Osteoid-Osteoma": Benign Osteoblastic Tumor Composed of Osteoid and Atypical Bone, *Arch. Surg.* **31**:709-728 (Nov.) 1935.

375. Jaffe, H. L., and Lichtenstein, L.: Osteoid-Osteoma: Further Experience with This Benign Tumor of Bone, with Special Reference to Cases Showing Lesion in Relation to Shaft Cortices and Commonly Misclassified as Instances of Sclerosing Non-Suppurative Osteomyelitis or Cortical Bone Abscess, *J. Bone & Joint Surg.* **22**:645-682 (July) 1940.

In interpreting the roentgenogram in a case of osteoidosteoma, they caution that this picture has two aspects: the manifestation of the osteoidosteoma proper and that of the reaction it has incited in the surrounding tissue. The osteoidosteoma proper is usually indicated by a relatively radiolucent or rarefied area, although if it has become substantially ossified it may appear as a relatively radiopaque nidus. One may have difficulty in distinguishing the shadow of the osteoidosteoma in the cortex of a long bone if the thickening of the cortex is considerable or if the lesion has become ossified, since this shadow may be dominated by that of the thickened cortex.

Lichtenstein and Jaffe³⁷⁶ believe they have presented a new bone tumor and give to it the name "eosinophilic granuloma" because of the presence of many eosinophilic polymorphonuclears. They feel it may be a virus granuloma, that it is benign and that it is cured by wide excision. The tumor occurs in young persons, especially boys and young men, and mainly involves the calvarium, but it may occur in other bones such as the ribs and the femur. The onset is sudden, with pain, swelling and tenderness. Roentgen examination shows a localized lesion starting in the medullary cavity and expanding and eroding the cortex. The course is rather rapid. The tissue of the tumor is yellowish or brownish and its microscopic appearance is characterized by phagocytosed eosinophils. Giant cells are likewise present. There may be an eosinophilia of the blood, and a sternal biopsy may show many eosinophilic cells.

Malignant Tumors Associated with Bone Diseases.—New growths are frequently superimposed on previously existing lesions. Sarcoma is not infrequently observed as a late manifestation in Paget's disease. Wolfe and Black³⁷⁷ report an interesting case of Paget's disease with a superimposed intracranial neoplasm. The autopsy showed a thickened and spongy calvarium and a large and misshaped skull due to the enlarged frontal, parietal and occipital bones. Attached to the basal dura on the left side and extending posteriorly from the superior petrous border to the posterior fossa, there was a partially calcified spherical tumor 5 by 4 by 3 cm. This tumor compressed the cerebellum. The tumor tissue was reported to resemble sarcoma and to be a neoplastic process arising in association with Paget's disease.

Jewell and Lofstrom³⁷⁸ report a case of associated fragilitas ossium and osteogenic sarcoma. Although these 2 conditions occurred together, it is not felt that there was any direct relation between the 2. The

376. Lichtenstein, L., and Jaffe, H. L.: Eosinophilic Granuloma of Bone, with Report of Case, *Am. J. Path.* **16**:595-604 (Sept.) 1940.

377. Wolfe, A. M., and Black, W. C.: Paget's Disease: Report of Case with Intracranial Neoplasm, *Rocky Mountain M. J.* **37**:586-587 (Aug.) 1940.

378. Jewell, F. C., and Lofstrom, J. E.: Osteogenic Sarcoma Occurring in Fragilitas Ossium: Case Report, *Radiology* **34**:741-743 (June) 1940.

should warrant treatment by curettage, curettage and bone grafting, or excision and bone grafting. He has used block or massive resection in cases of recurrent giant cell tumor with what he calls "local malignancy" and in cases in which the tumor was of the "aggressive type" with clinical and roentgenographic indications that it was malignant. The defect in the bone is filled in to preserve the form. Amputation is done only when the patient is first seen in a far advanced stage, when there has been infection after a previously unsuccessful curettage or when there are positive signs that the tumor is malignant.

After treating primary sarcoma of bone by irradiation, Brunswick and Tschetter³⁸⁸ have followed a series of 20 patients without detecting clinical evidence of metastatic lesion. All the patients were unable to undergo or refused operation. In all cases diagnosis was confirmed by biopsy, and only conservative surgical intervention and irradiation or irradiation alone was used. Of these 20 patients, 6 have survived for three years or more without clinical evidence of extension of the disease. The authors' conclusion is that "an extremely pessimistic attitude regarding the value of irradiation in benefiting cases of primary bone tumor is not justified."

Phemister³⁸⁹ in discussing conservative treatment of bone tumors reports 6 carefully selected cases of malignant primary bone tumor without demonstrable metastases. The tumors were well localized. They were treated by local excision and roentgen irradiation. One patient died of pulmonary metastasis without local recurrence, and 5 showed no recurrence after periods ranging from seventeen months to fourteen years. He urges more conservative procedures in carefully selected cases.

Ferguson³⁹⁰ has made a detailed statistical study of 400 cases of osteogenic sarcoma reported in the Registry of Bone Sarcoma of the American College of Surgeons. As a result of this study, he recommends the following treatment for osteogenic sarcoma: (1) avoidance of early amputation ("Early amputation is defined as amputation before the seventh calendar month after onset of symptoms."); (2) irradiation before delayed amputation; (3) irradiation, excision and implantation of a bone graft or bone chips before amputation, with amputation before the recurrence becomes evident; repetition of excision, rather than amputation, if recurrence becomes evident before amputation can be done.

388. Brunswick, A., and Tschetter, D.: *Experiences in Treatment of Primary Skeletal Sarcoma by Irradiation*, *Am. J. Roentgenol.* **44**:83-89 (July) 1940.

389. Phemister, D. B.: *Conservative Surgery in Treatment of Bone Tumors*, *Surg., Gynec. & Obst.* **70**:355-364 (Feb., no. 2A) 1940.

390. Ferguson, A. B.: *Treatment of Osteogenic Sarcoma*, *J. Bone & Joint Surg.* **22**:916-922 (Oct.) 1940.

XII. CONDITIONS INVOLVING THE LOWER PART OF THE BACK

Causation.—In an unusually comprehensive discussion of the spine from the anatomic, embryologic and physiologic points of view, Carey³⁹¹ correlates pain in the lower part of the back with scoliosis. He presents as illustrations many photographs of a "dynamic muscle-bone balance model of the human spine." It is stated that with only thirteen pairs of spinal muscles there are more than sixty-seven million possible combinations of muscular unbalance capable of producing lateral curvature. [Ed. NOTE: This is a good article in spite of the unbelievable figures.]

To learn the relation of anomalies in the lower part of the back to injury, Connell³⁹² studied a group of 6,391 zinc miners over a period of five years. Anteroposterior roentgenograms were taken of the lumbar and sacral area, and 12.85 per cent of these miners were found to have spina bifida occulta of the sacrum or of the fifth lumbar vertebra. During the five year period 199 received injuries to their backs; this figure included only those who felt a sudden catching pain while doing ordinary work. Those with external trauma were not included. Of the 199 injured, 172 had been submitted to roentgen examination, and spina bifida occulta had been demonstrated in 10.13 per cent of these. Thus the incidence of anomalies in the lower part of the back was less in the injured group than in the series as a whole. It was also determined that 20.29 per cent of the patients with normal spines had prolonged periods of healing or became subjects of litigation, compared with 10.53 per cent of the patients with spina bifida occulta. The author concludes that "spina bifida occulta is not a predisposing cause of simple back strain, and that it does not effect a prolonged healing period in individuals who have received injury to the spine." [Ed. NOTE: This information should be of great importance to the industrial surgeon from the medicolegal point of view.]

A report by Carmichael³⁹³ asserts that the most common cause of sciatica is one or more of the following pathologic conditions of the anus: a small pile in the posterior quadrant, a slight posterior prolapse, a buried fissure, a posterior crypt or a posterior papilla. The nervous connection of the anal sympathetic and parasympathetic nerve supplies to the sciatic nerve is traced, and the radiation of sciatica is explained on a reflex basis. Four cases are presented which illustrate the almost immediate relief of the sciatic pain after treatment of the associated lesion or lesions of the anus. [Ed. NOTE: Lesions of the anus should be checked. Some of the author's statements seem a little far fetched.]

391. Carey, E. J.: Low Back Pain: Symposium; Anatomic Aspect. Wisconsin M. J. **39**:427-446 (June) 1940.

392. Connell, M. A.: Relationship of Spina Bifida Occulta to Back Injury. J. Oklahoma M. A. **33**:9-11 (July) 1940.

393. Carmichael, E.: Common Cause of Sciatica. M. Rec. **152**:8-10 (July 3) 1940.

Smith³⁹⁴ reports 13 cases in which no other explanation could be found for sciatica than the hyperglycemic response to the one hour-two dose dextrose tolerance test. The patients presented themselves for relief of the sciatic pain and gave no history suggestive of diabetes. In 7 patients the pain had been present for one month or less; in 6 it had been present for from several months to several years. One patient was not improved by a diet and treatment with vitamin B₁ (thiamine) and insulin, another patient was improved but not relieved, and the remaining 11 patients were relieved of their pain. The diet consisted of 120 Gm. of carbohydrate, 80 Gm. of fat and 80 Gm. of protein. Ten units of insulin each day was used (except in 3 cases in which only the diet and the vitamin B₁ were used). The amount of the dose of vitamin B₁ is not stated. It has been shown that an increase in caloric intake requires an increase in vitamin B₁ intake, and the author offers a tentative explanation for neuritis associated with hyperglycemia as follows: Unmetabolized carbohydrate may enter into some combination with vitamin B₁ and withdraw it from the tissue or may exert some inhibiting influence on it. [Ed. NOTE: This possible explanation of sciatic pain merits consideration. The information is from a reliable source.]

Disability from disease in the lower part of the back is becoming one of the most frequent grounds for claiming compensation in industry. Johnstone³⁹⁵ reports a series of 3,018 cases of pain in the lower part of the back; many ages, races and social levels and many types of industry are represented. The study was made from April 1936 to February 1939. The contrast of the rejections on the grounds of the condition not being of occupational origin in 1936 (40 per cent) to those in 1939 (71 per cent) is understood when it is noted that in 1937 a policy of unlimited laboratory investigation was adopted. In addition, complete histories were obtained and physical examinations made. This policy of complete study resulted in finding (in over 70 per cent) pathologic conditions which when considered with a negligible history of injury formed a basis of rejection. The author states, "From the internists' viewpoint the so-called 'industrial back' is not primarily an orthopedic problem. It is one for differential diagnosis." [Ed. NOTE: This is another good article for the industrial surgeon.]

Diagnosis.—That sciatica is of a reflex nature in a considerable number of cases is brought out by Steindler.³⁹⁶ He states that recognition of this fact is essential for rational diagnosis and treatment of the underlying condition. Most strains in the lower part of the back result

394. Smith, C. T.: Sciatic Pain and Hyperglycemic Response to Glucose Tolerance Test, *North Carolina M. J.* 1:315-317 (June) 1940.

395. Johnstone, R. T.: Industrial Back from Internist's Viewpoint, *Am. J. Surg.* 48:544-547 (June) 1940.

396. Steindler, A.: Interpretation of Sciatic Radiation and Syndrome of Low Back Pain, *J. Bone & Joint Surg.* 22:28-34 (Jan.) 1940.

from serious injuries to soft tissues. The author mentions six patterns of pressure or "trigger points" which indicate typical syndromes. These are as follows:

1. The sacrospinalis syndrome, producing a pressure point at the posterior superior or inferior iliac spine.
2. The lumbosacral syndrome, with a pressure point at the lumbosacral junction.
3. The gluteal syndrome, producing a pressure point at the gluteus maximus insertion.
4. The transversosacral syndrome, with a pressure point at the transversosacral articulation in cases of sacralization of the fifth lumbar vertebra.
5. The tensor fasciae latae syndrome, with the tender point at the lateral border of the fascia and iliotibial band and a positive Ober sign.
6. The myofascial syndrome, with vague tenderness along the sacrospinalis muscle and its fascial sheath.

Irritation of these trigger points aggravates radiation of the sciatica; injection of procaine hydrochloride eliminates such radiation.

[ED. NOTE: This article should be studied. The real value of the author's "trigger points" will be determined by the report of experiences in other clinics.]

When there is pain in the lower part of the back for which no local cause can be demonstrated, the genitourinary system should be thoroughly investigated. Culver³⁹⁷ discusses this subject. The tendency of low lying kidneys to produce pain is made especially evident when it is observed that they have a high incidence of deficient emptying power, characterized clinically by varying degrees of hydronephrosis. The pain is most often localized in front, but it may be present in the back alone, or there may be a combination of the two. Renal calculi, neoplasms and infections and bladder lesions present varied clinical pictures of pain in the lower part of the back or in the pelvis. Pain in the back from diseases of the prostate gland and the seminal vesicles may be caused (1) by a metastasis of the infection or the neoplasm to the spine, (2) by blood-borne toxins arising from infections in these structures or (3) by reflex nervous impulses arising from pressure or adhesions within the structures. Pain referred from the prostate gland and the seminal vesicles may occur over one or both sacroiliac joints, in the low dorsal or high dorsal regions of the spine. The pain is variously described as an ache, a dull pain, a soreness, a stiffness, a burning or a bearing down pain. Pain originating in the seminal vesicles is aggravated by pressure on that structure. Other implicated urologic conditions are chronic urethral conditions in women, metastasis from testicular neoplasms and varicocele. [ED. NOTE: This is an excellent review.]

397. Culver, H.: Low Back Pain: Symposium; Urologic Aspect, Wisconsin M. J. 39:450-456 (June) 1940.

Treatment.—In an article on the manipulative treatment of backache Jostes³⁹⁸ stresses that it is contraindicated in all definitely pathologic conditions of the lower part of the back and should not be employed until these have been ruled out. Definite manipulations are carried out with the patient on the floor without anesthesia. Preliminary massage of the gluteal muscles and of the lumbar area relaxes spasm. Nine well planned maneuvers are described and illustrated, and a strict postoperative regimen of rest, exercise, heat and support is established. [Ed. NOTE: This work of Jostes confirms a great many ideas of the late W. S. Baer.³⁹⁹ Orthopedic surgeons give too little attention to manipulation. The author is to be congratulated on his work.]

By far the most common cause of backache is chronic postural strain, and for this condition physical therapy is of cardinal importance. Krusen⁴⁰⁰ outlines the treatment as follows:

- (1) Rest in bed with a fracture board on the springs and a firm hair mattress.
- (2) Traction of 4 to 8 pounds (1.8 to 3.6 kg.) on each leg [which hyperextends the spinal column].
- (3) A padded sling under the lumbar region of the spinal column. . . .
- (4) Daily local applications of radiant heat and deep sedative massage, usually alternating with diathermy and massage.
- (5) Occasional epidural injections if there is sciatic pain and if relief of pain is not obtained by traction.
- (6) Finally, manipulation through an extended normal range under general pentothal sodium anaesthesia if previous treatment has failed to elicit a favorable response.

The author states that he has rarely noted more than temporary relief after manipulation but that this form of treatment possibly merits further consideration. [Ed. NOTE: This is an excellent article on conservative therapy.]

Hoffman⁴⁰¹ has examined a large number of women complaining of chronic pain in the lower part of the back and has found in a great number a hard nodule situated posteriorly over one or both sacroiliac joints. When pressure is applied over the nodule, the pain is reproduced. One case is reported in which complete relief was obtained after excision of the one nodule found. Pathologic examination of the tissue showed nerve tissue, but the exact type was not determined.

398. Jostes, F. A.: Backache: Manipulative Treatment Without Anesthesia, Mississippi Valley M. J. **62**:114-118 (July) 1940.

399. Baer, W. S.: Sacro-Iliac Strain, Bull. Johns Hopkins Hosp. **28**:15 (May) 1917.

400. Krusen, F. H.: Backache: Relation of Physical Therapy to Its Management, Canad. M. A. J. **42**:534-541 (June) 1940.

401. Hoffman, J. M.: Low Back Pain, J. Florida M. A. **27**:30-31 (July) 1941.

Rupture of Intervertebral Disks.—(a) Clinical Findings: A study of 100 cases is reported by Macey.⁴⁰² In 23 of these there was a history of adequate injury. In 9, the patient was not aware of injury but complained of sciatic pain coming on while standing with the spine in flexion. In 68 cases there was no association with injury. Of the 23 cases in which there was a history of injury, both backache and sciatica, usually continuous, were present in 9. In 2 there was continuous sciatic pain alone, and in 12 there was a history of backache with late onset of sciatica of many years' duration. Of the 68 cases in which there was no associated injury, persistent backache and sciatica were present in 13. In 13 there was a long history of backache and recurrent sciatic pain and in 34 a history of backache and later of persistent sciatic pain alone for many years. A detailed account of the physical observations is given in this report.

Keegan and Finlayson⁴⁰³ report the clinical observations on 40 patients operated on by laminectomy. Seventy per cent of the patients complained of strain of the back. In 50 per cent the ankle jerk reflex was reduced, and in 55 per cent sensation in the affected leg was diminished. Motor power was reduced in 27.5 per cent, and control of the sphincters was affected in 7.5 per cent. In only 10 per cent of the patients was a block of the flow of spinal fluid demonstrated.

Thirty-five cases in which herniated intervertebral disks were found at operation are reported by Toumey.⁴⁰⁴ The average duration of symptoms from the time of the first attack to the time of operation was five years. Five of the patients had bilateral and 30 unilateral sciatic pain. Paresthesias were present in 75 per cent, unilateral weakness of the leg in 69 per cent, and pain on coughing or sneezing in 52 per cent. Ninety per cent of the patients showed Lasègue's sign.

Williams⁴⁰⁵ states that changes within the lumbosacral and less frequently in other lumbar intervertebral disks are undoubtedly the cause of symptoms in more than 90 per cent of patients having symptoms of pain in the lower part of the back and sciatica. Acute rupture of a disk usually occurs between the ages of 10 and 25 years and is the result of a definite compressive injury. Chronic destruction of a disk results from uneven distribution of weight at the lumbosacral junction. Increased lordosis, a lateral tilt, fragmentation of the facets and over-riding the facets are mentioned as the causative factors. It is the author's opinion that in more than 95 per cent of the cases pain in the lower part

402. Macey, H. B.: Clinical Aspects of Protruded Intervertebral Disk. *Arch. Surg.* 40:433-443 (March) 1940.

403. Keegan, J. J., and Finlayson, A. I.: Low Back and Sciatic Pain Caused by Intervertebral Disk Herniation, *Nebraska M. J.* 25:179-184 (May) 1940.

404. Toumey, J. W.: Intervertebral Disk Protrusion, *Lahey Clin. Bull.* 1:11-16 (Jan.) 1940.

405. Williams, P. C.: Low Back Pain, *South. M. J.* 33:788-797 (Aug.) 1940.

of the back is due to mechanical alterations which have resulted in constriction of the foramen and an impingement on the nerve root rather than to prolapse of the disk itself. [Ed. NOTE: Many will undoubtedly agree with the author's statements which are the result of many years of experience.]

(b) Diagnosis: Spurling and Grantham⁴⁰⁶ present the differentiating points by which the interspace in which the rupture of a disk has occurred may be determined. When there is a rupture of the disk in the third lumbar interspace, one finds tenderness to deep pressure over the third lumbar spine or lamina; compression of the jugular veins produces paresthesias in the fourth and the fifth lumbar dermatomes. There are reduction or absence of the knee jerk reflex and hypesthesia and paresthesias in the fourth and fifth lumbar dermatomes. With rupture of the disk in the fourth lumbar interspace there are tenderness over the fourth spinous process and paresthesias in the fifth lumbar and first sacral dermatomes; knee and ankle jerk reflexes are not affected. With rupture of the disk in the fifth lumbar interspace there are tenderness in the region of the fifth lumbar vertebra, paresthesias in the first and second sacral dermatomes and diminution or absence of the ankle jerk reflex.

According to Hampton,⁴⁰⁷ a diagnosis of herniation of an intervertebral disk was established in 133 cases with an accuracy of 93 per cent by roentgen examination after injection of iodized oil into the spinal subarachnoid spaces. Nevertheless, he advises that air myelography be used first, even though its accuracy is probably not over 50 per cent. It is reliable when the findings are unequivocally positive, and its use may obviate in about half the patients the injection of iodized oil, which is a foreign body and in some instances has produced symptoms. He warns against following air myelography with an injection of iodized oil before the air has been absorbed and a normal flow of spinal fluid reestablished. He describes a technic of roentgen examination in detail.

Wartenberg⁴⁰⁸ believes that since myelography is neither absolutely harmless nor absolutely decisive it should not be a routine neurologic procedure. He would reserve it as a last resort in the comparatively rare cases in which the "whether" or the "where" of surgical intervention cannot be decided by clinical neurologic methods.

406. Spurling, R. G., and Grantham, E.: Low Back and Sciatic Pain Caused by Rupture of Intervertebral Disc With or Without Herniation of Nucleus Pulposus, *Internat. Clin.* 4:251-266 (Dec.) 1940.

407. Hampton, A. O.: Iodized Oil Myelography: Use in Diagnosis of Rupture of Intervertebral Disk into Spinal Canal, *Arch. Surg.* 40:444-453 (March) 1940.

408. Wartenberg, R.: Remarks on Myelography, *J. Nerv. & Ment. Dis.* 91:47-52 (Jan.) 1940.

[ED. NOTE: The ideal substance for use in myelography has not yet been found.]

(c) End Results: Of the 40 patients operated on by laminectomy in Keegan and Finlayson's ⁴⁰³ series, 60 per cent had definitely herniated disks, and 25 per cent had a thickened ligamentum flavum with a protruded disk. Their end results were graded according to the degree of recovery. In 57.5 per cent of the cases there was 90 to 100 per cent recovery; in 17.5 per cent there was 80 to 90 per cent recovery, and in 10 per cent there was a 50 per cent recovery. Failure to have any recovery occurred in 15 per cent. Toumey ⁴⁰⁴ classified 31 of his patients on whom operation had been performed according to end results after an average period of eight months. Twenty were rated as having excellent results; 3, good; and 8, poor. Williams ⁴⁰⁵ reported relief of sciatica without operation in 90 per cent of his cases. His conservative management consisted in correcting the lordosis and relieving the tight muscles and fasciae of the anterior and lateral aspects of the thigh. Facetectomy and grafting were done on 32 patients in whom the condition was resistant, and relief of segmental symptoms was obtained in all but 1, who died after operation. Mixter and Barr ⁴⁰⁹ report 123 consecutive cases in which operation was performed. One patient died after operation. They followed 77 of the patients one year or more and reported the results as good in 80 per cent, fair in 10 per cent and poor in 10 per cent. [ED. NOTE: All these reports of end results are establishing this as an accepted disease entity.]

Spondylolisthesis.—Hitchcock ⁴¹⁰ presents 3 cases of definite progressive anterior displacement of the last lumbar vertebra. In none of the cases was trauma a significant feature. In each case there was increasing thinning of the disk. Interruption of the continuity of the neural arch occurs in 5 to 6 per cent of persons, and this is the fundamental lesion which precedes and causes spondylolisthesis. The author reviews the evidence that a defect in the narrow isthmus or interarticular portion of the neural bow at the junction of the pedicle and the lamina is of congenital origin and the result of separate centers of ossification; he concludes that it is insufficient to prove this popular theory. He produced fractures through this isthmus by flexing fetal spines but was unable to do so by extending them and suggests that trauma during delivery or shortly afterward may be the cause of this defect. [ED. NOTE: This article should be read in full; it is one of the best on spondylolisthesis written in many years.]

409. Mixter, W. J., and Barr, J. S.: Protrusion of Lower Lumbar Intervertebral Disks, *New England J. Med.* **223**:523-529 (Oct. 3) 1940.

410. Hitchcock, H. H.: Spondylolisthesis: Observations on Its Development, Progression, and Genesis, *J. Bone & Joint Surg.* **22**:1-16 (Jan.) 1940.

III. CONDITIONS INVOLVING THE SPINE AND THORAX, EXCLUSIVE OF THOSE IN THE LOWER PART OF THE BACK

Scoliosis.—(a) Causes: Bisgard and Musselman⁴¹¹ believe "that inequality of growth on the 2 sides of the vertebral bodies plays a major rôle in the production and progression of idiopathic scoliosis. If not the primary etiological factor, as it may well be, it is an important contributing factor." They present experimental data to show that scoliosis can be produced in kid goats by arresting the growth of the epiphyses of the vertebral bodies on one side. In their discussion the question is raised, "If unilateral growth retardation is the sole factor responsible for idiopathic scoliosis, what causes this unilateral retardation of growth?" and they suggest that "among the theoretically possible causes are epiphysitis or epiphyseodystrophy and congenital abnormality of the cartilage." [Ed. NOTE: While the growth or unequal growth of the vertebral epiphyses may well be a factor in some cases of scoliosis, it seems unlikely that this is the primary cause of so-called idiopathic scoliosis. It is frequently pointed out that idiopathic scoliosis increases during the period of growth, but it is seldom mentioned (if it is recognized) that in growing children with idiopathic scoliosis the curve does not always increase when the spine grows longer. There are other objections to the theory that unilateral retardation of growth is the cause of idiopathic scoliosis, and it is questionable that epiphysitis may be a cause of this unilateral retardation of vertebral growth, especially when it is remembered that in most children with this disease of the vertebrae dorsal round back tends to develop, and lateral curvature, if present at all, is always the lesser problem.]

The experimental production of scoliosis by Haas⁴¹² and Bisgard and Musselman is of special interest. The former worked with dogs and the latter with kid goats. They have shown that growth in the length of vertebrae is derived from the proximal and distal epiphysial growth cartilages. They were able to produce lateral curvatures experimentally by injuring the epiphysial plate. Haas was able to prevent this deformity by vertebral fusion after the injury. He points out that there is a definite tendency toward lordosis after fusion of the spine in growing animals, that lordosis may correct existing kyphosis and that in cases of tuberculosis of the spine there may be a lessening of the deformity after fusion. [Ed. NOTE: It should be added that this result may be due partly to the removal of the prominent spinous processes. If

411. Bisgard, J. D., and Musselman, M. M.: *Scoliosis: Its Experimental Production and Growth Correction; Growth and Fusion of Vertebral Bodies*, Surg., Gynec. & Obst. **70**:1029-1036 (June) 1940.

412. Haas, S. L.: *The Prevention of Deformity of the Spine by Vertebral Fusion*, J. Bone & Joint Surg. **22**:157-160 (Jan.) 1940; *Influence of Fusion of the Spine on the Growth of the Vertebrae*, Arch. Surg. **41**:607-624 (Sept.) 1940.

there is any real growth in the anterior vertebral area over the fused area, it may well be only in the part fused above or below the involved vertebrae, for it is well known that the epiphyses are frequently so involved that no further growth of the vertebral body is possible. Frequently, the whole development of the patient is retarded, and the growth of the entire spinal column may be relatively slight.] Haas states that this corrective influence (tendency to lordosis) should be borne in mind in the treatment of vertebral epiphysitis (kyphosis dorsalis juvenilis). [Ed. NOTE: This seems to be an important suggestion, since it is well known that operation for fusion of the spine is usually performed too late to obtain the desirable cosmetic correction.] Haas states,

The effect of fusion of the spine on a very young growing person needs careful study. It is possible that in some cases it may aggravate rather than decrease the deformity. Therefore, it is important to select the proper region of the spine, the correct age for fusion and the proper number of vertebrae to fuse.

[Ed. NOTE: It might be added that the position of the spine when fusion is done is also important. In some cases of paralytic scoliosis in which the curve is increasing in spite of all conservative treatment, it might be possible by fusing the spine in a position of slight flexion to prevent or limit the development of objectionable lordosis during later years of growth, especially if the patient is young at the time of fusion.]

Haas states: "With the Albee type of operation if the markers are attached to the graft there is no separation of the markers, because there is no interstitial growth in a graft. The grafted region may be increased to some extent if bone is added to either end by a proliferation of osseous tissue adjoining the grafted area." Bisgard and Musselman, however, conclude that "under the influence of a distracting force, bone, that is, grafted bone is capable of intrinsic growth in length."

[Ed. NOTE: The experimental observations of Haas that growth of the fused area of the spine is definitely retarded and that deformity (lordosis) may develop as the child continues to grow is important. It has been pointed out by other workers for years that the spine continues to grow after fusion; some even believe that its growth is retarded relatively little if at all. Probably the rest of the spine continues to grow, but the fused area grows little, if at all, in most cases. The correction of the curvature usually gives the patient a definite increase in height.]

(b) Treatment: Bisgard and Musselman state:

From the . . . experimental evidence that growth on one side of vertebrae can be arrested by removal of portions of the epiphyseal growth cartilages on that side, the possibility of accomplishing correction of curvatures of idiopathic scoliosis in suitable cases by this means suggests itself. The type of case which would seem suitable for this proposed form of treatment would be a child who has a moderate curvature and several years in which to grow. With growth

arrested on the side of convexity in several vertebrae at or near the apex of the curvature, any increase in length on the side of concavity should bring about some correction of the curvature.

They believe that with resection of segments of two ribs it should be possible to expose six or more of the vertebral bodies in a patient with scoliosis. [ED. NOTE: Besides the technical difficulties of the treatment proposed one might mention that it is questionable whether as much correction of curvature could be obtained in this way as by the method now used, that is, correction in a turnbuckle jacket followed by fusion of the spine. It is likely that only mild curvatures could be corrected sufficiently by growth of the concave side, and it is doubtful whether any operation at all is indicated for these. For larger curvatures correction followed by fusion would probably give better results.]

Anatomic Variations of the Spine and Thorax.—Most congenital malformations of the spine have been described in the literature. However, Mayoral⁴¹³ describes a congenital malformation of the transverse process of the first dorsal vertebra which apparently has not been previously reported. He presents 1 case in which the anomaly had been considered an ununited fracture. On reviewing 5,632 roentgenograms he found 4 additional cases in which there was nonunion of the transverse process of the first dorsal vertebra; in 2 there was bilateral nonunion and in 2 there was nonunion of the left process. Because of possible medicolegal or compensational aspects it may be important to recognize this apparently rare variation.

Schüller⁴¹⁴ discusses "basilar impression" or "basilar invagination," terms generally used to designate different types of deformities involving the posterior cranial fossa and the upper cervical vertebrae. He describes three types due to (1) an abnormal structure of the skeleton, as in decalcification of the bone in rickets or Paget's osteitis deformans, (2) long-standing increased intracranial pressure causing atrophy of the cranial capsule (e. g. hydrocephaly) and (3) congenital malformation in the atlanto-occipital region (assimilation of the atlas). The anatomic findings in the different types are variable. As a rule the weighted parts of the occiput forming the foramen magnum are pushed up toward the cranial cavity (whence the term "basilar impression"). Clinically there is the characteristically short neck, often combined with a caput obstipum (wryneck). Movements of the head are usually free, and there is no fixation of the neck as in Pott's disease. There may be no untoward symptoms during the life of some patients, but others may

413. Mayoral, A.: Congenital Malformation of the Transverse Processes of the First Dorsal Vertebra, *Radiology* 35:82-83 (July) 1940.

414. Schüller, A.: Diagnosis of "Basilar Impression," *Radiology* 34:214-216 (Feb.) 1940.

show severe symptoms owing to compression of the spinal cord. The symptoms are usually slowly progressive with occasional acute exacerbations. The most common erroneous diagnosis in cases of basilar impression are: occipital neuralgia, syringomyelia, syringobulbia, the Klippel-Feil syndrome and cerebellar tumor. Decompressions are occasionally done with the mistaken idea that cerebellar tumor is present. The author points out that the characteristic deformities of the posterior cranial fossa and of the upper cervical vertebrae are well seen in lateral and anteroposterior roentgenograms, which help one to avoid an erroneous diagnosis and a dangerous and unnecessary operation.

Infectious Lesions of the Intervertebral Disks.—Ghormley, Bickel and Dickson⁴¹⁵ "emphasize the occurrence of a lesion of the spine involving principally the intervertebral disks with a more or less severe febrile onset, as a rule, denoting in all probability a primary or secondary infectious process as the underlying cause." They differentiate this condition from osteomyelitis of the spine and present a good differential diagnosis covering tuberculosis, osteomyelitis, typhoid spine, *Brucella abortus* infection, traumatic injury to the disk, congenital absence of the disk and fusion of the vertebrae. They feel that a preexisting infection is often, if not always, necessary and that the lesion itself is a metastatic infection incidental to dissemination of a preexisting infection through the blood stream. The clinical findings were pain, spasm of muscles, limitation of motion and tenderness, and some of the patients were severely ill with elevation of temperature and prostration. This condition must be especially differentiated from true osteomyelitis of the spine with the formation of an abscess requiring drainage and particularly from osteomyelitis of the vertebrae which may be complicated by neurologic manifestations and demand laminectomy and drainage of a localized abscess.

The syndrome is similar to osteomyelitis of the spine, but because of the minor involvement of the vertebrae and the apparently infrequent suppuration we feel that the condition should be regarded as a separate entity. This is probably the same condition as was seen in some cases of "typhoid spine" and as may be seen in the course of infections with *Brucella abortus*. The prognosis both as to life and prevention of disability is excellent in most cases. Treatment should be by conservative orthopedic measures, surgical procedures seldom being indicated.

Osteochondritis Vertebralis.—Fawcitt⁴¹⁶ reports a case in which osteochondritis vertebralis (Calvé) was associated with pathologic cystic

415. Ghormley, R. K.; Bickel, W. H., and Dickson, D. D.: A Study of Acute Infectious Lesions of the Intervertebral Disks, *South M. J.* 33:347-353 (April) 1940.

416. Fawcitt, R.: Osteochondritis Vertebralis (Calvé) Associated with Pathological Changes in Other Bones, *Brit. J. Radiol.* 13:172-178 (May) 1940.

changes in other bones, a condition which evidently has not been previously described and of which the exact significance is not yet known. He studied the case carefully, taking roentgenograms monthly and investigating the whole skeleton. He points out that the distribution of the cystic changes is noteworthy; they were seen in the head, neck and proximal portions of the shafts of the long bones in which they occurred (femur and humerus). There was no evidence of any bending of these bones, and cystic changes were not distributed throughout the shafts as in general osteitis fibrosa.

Tetanus and Deformities of the Spine.—Dietrich, Karshner and Stewart⁴¹⁷ discuss the problem of tetanus and lesions of the spine in children. They note that with the increase in the number of recoveries there has also been an increase in the number of patients showing vertebral deformities. They suggest the possibility of preventing at least some of these deformities by early and vigorous sedation. Examination of 9 of 13 patients who had had tetanus in childhood showed compression of thoracic vertebrae without a demonstrable fracture line. One vertebra was involved in 2 cases; two vertebrae in 1 case; three vertebrae in 2 cases; four vertebrae in 2 cases; five vertebrae in 1 case, and six vertebrae in 1 case. The fifth dorsal vertebra was involved in 8 cases; the sixth in 7 cases; the ninth in 2 cases; the eighth in 4 cases; the fourth in 2 cases, and the seventh in 6 cases. In the cases in which there was least involvement, the compression was limited to the anterior portion of the vertebral body. In the cases in which there was more severe involvement, the entire vertebral body was compressed from above downward. Most of the affected bodies were wedge shaped. In those cases in which involvement was most severe, the density of the compressed bodies was increased. The intervertebral spaces were unchanged. The upper and the lower borders were smooth and straight except in the bodies most severely affected, in which they were slightly concave in lateral projection. In some instances the compression reduced the height of the body to less than half of normal. The involvement centered about the fifth and sixth thoracic segments, extending as high as the fourth and as low as the ninth, thus differing in location from kyphosis dorsalis juvenilis, in which the changes are most severe in the eighth and ninth thoracic vertebrae and always limited to the lower half of the thoracic spine. The authors give a good differential diagnosis and disagree with the explanation of the mechanism of the deformity as described by Roberg⁴¹⁸ in 1937. They believe the dorsal portion of the

417. Dietrich, H. F.; Karshner, R. G., and Stewart, S. F.: *Tetanus and Lesions of the Spine in Childhood*, J. Bone & Joint Surg. **22**:43-54 (Jan.) 1940.

418. Roberg, O. T., Jr.: *Spinal Deformity Following Tetanus and Its Relation to Juvenile Kyphosis*, J. Bone & Joint Surg. **19**:603-629 (July) 1937.

spine is not flattened in the opisthotonic position but that all the normal spinal curves are increased, the muscles tending to approximate their ends and along an axial line approximating the occiput and the pelvis, with the greatest force exerted on the apical bodies of the thoracic vertebrae.

Epiphyses and Growth.—Nathan and Kuhns⁴¹⁹ report 75 cases in which epiphysitis of the spine was studied during the course of the disease. They describe the end results in 27. The diagnosis was confirmed roentgenologically in every case. The patients were 50 women and 25 men. The authors separate the condition into three stages: early, healing, healed. The healed stage is reached when the epiphyses are united and the deformities are fixed in varying degrees. The changes seen at this stage remain constant throughout life. In 60 cases there was involvement of the thoracic area; in 13, of both the thoracic and the lumbar area; in only 2, of the lumbar area. The authors believe that early treatment can prevent deformity, and they recommend exercises, rest and good hygiene; if this is unsuccessful, then a plaster jacket with the spine in as much extension as possible. [ED. NOTE: The problem of vertebral epiphysitis is still a difficult one, and many patients are seen too late to prevent deformity. The deformity is often severe and probably in many cases could be efficiently prevented only by early fusion of the involved vertebrae. It seems that most fusions are done too late to prevent the increasing deformity or to gain correction by the possible growth of the anterior elements of the vertebrae after the fusion has stopped the growth of the posterior elements.]

MacGowan⁴²⁰ in a paper on the roentgen examination of normal spines and of kyphotic spines of adolescent persons describes the normal standards for the roentgenographic appearance of the spines of patients 8 to 19 years of age, a period of rapid growth which presents roentgenographic peculiarities, more manifest in the spinal than in any other osseous growth. He describes the appearance of the spinal column at birth, at 7 years of age, at 10 years (at this time the epiphysal rings appear), at 13 years and at 18 to 25 years. He traces the stages (as he sees them) and believes that the active stage lasts from one to two years and that it is self limiting. The final healed or arthritic stage is characterized by cuneiform ossification of the disk. [ED. NOTE: The adolescent kyphotic spine presents a difficult and important orthopedic problem. In many instances it is treated over a period of years, often long after any treatment is necessary. Most orthopedic surgeons do

419. Nathan, L., and Kuhns, J. G.: Epiphysitis of the Spine, *J. Bone & Joint Surg.* 22:55-62 (Jan.) 1940.

420. MacGowan, T. J. B. A.: Radiologic Examination of Normal and Adolescent Kyphotic Spines, *Glasgow M. J.* 133:206-209 (June) 1940.

not know just when to stop treatment. Many feel that the condition continues to increase up to the age of 19 or 20. The difficulty is in knowing the time and point beyond which no further treatment is necessary. There still are no definite indications as to which lesions are going to progress to serious kyphosis and deformity (for which fusion of the spine is probably the only adequate treatment) and as to which will get along well with little, if any, increase in deformity.]

Gonadal Dysfunction and Vertebral Growth.—Lindgren⁴²¹ reports a study of the vertebral column in connection with the treatment of eunuchoidism in men and women. By roentgen examination he noted several open epiphyses in patients 32 years of age and thinks that the irregular ossification of epiphysial plates in the vertebrae (indicative of inhibited development) is probably due to gonadal hypofunction. Although the inhibited ossification did not produce a noticeable increase in the size of the vertebrae he feels that the extended growth of the long bones in contrast to the lesser growth of the vertebral column is a result of the persistence of the epiphyses and that this explains the typical eunuchoid proportions of the body. [ED. NOTE: This paper brings up the interesting problem of the effect of the gonads on the growth of the vertebrae and other bones. There are indications that sex factors may be important in various conditions such as adolescent or idiopathic scoliosis and kyphosis.]

Senile Osteoporosis.—Black⁴²² reports 208 cases, in 80 per cent of which the patients were women. The average age was 62 and the youngest 45 years. In this series the earliest symptoms were weakness, fatigue and dull backache for an average period of three years. The patient then usually suffered some trauma or had a spontaneous sensation of cracking in the back, followed by severe acute pain and later intermittent acute attacks of pain. The lower dorsal and lumbar regions were most commonly affected. The author points out that senile osteoporosis must be differentiated from fracture, metastatic tumor and myeloma.

Zacho⁴²³ reports only 3 cases but gives an excellent discussion of osteoporosis. After mentioning the characteristics and symptoms, he deals more fully with the cause of the disease. He believes that the cause of the primary form is nearly always a defect in diet (most

421. Lindgren, A. G. H.: *Vertebral Column and Eunuchoidism*, *Fortschr. a. d. Geb. d. Röntgenstrahlen* 60:448-456 (Dec.) 1939; abstracted, *J. A. M. A.* 14:1026 (March 16) 1940.

422. Black, J. R.: *Senile Osteoporosis*, *Proc. Staff Meet., Mayo Clin.* 15:619-623 (Sept. 25) 1940.

423. Zacho, A.: *Osteoporosis and Osteomalacia Columnae*, *Acta orthop. Scand.* 11:264-295, 1940.

frequently a deficiency of vitamin D). The secondary form may depend partly on disturbances in absorption (in diseases of the intestinal canal, the liver, the bile ducts and the pancreas), partly on disturbances in excretion (diseases of the kidney) and finally on disturbances of the internal secretions. In the form due to disturbances of absorption, defective absorption of vitamin D and possibly also of calcium salts is the most usual factor. Zacho discusses the similarity of senile osteoporosis, hunger osteomalacia and puerperal osteomalacia with involvement chiefly of the spine, the pelvis, the thorax and the shoulder girdle. He states that

it is now generally agreed that puerperal osteomalacia and rickets are in reality different results of the same cause. . . . The difference in the locality of the diseases is due to the fact that parts of the skeleton that grow most rapidly are those most attacked. This explains why it is principally the skull that is most attacked in childhood (rickets) amongst older children preferably the long bones (late rickets), and, after increase in height has ceased, the pelvis, spine and thorax (osteomalacia).

He believes that the basic factor in all these cases is a deficiency of vitamin D in the diet, because the function of this vitamin consists in facilitating the absorption of calcium from the intestinal tract as well as in retaining the absorbed calcium in the bone.

Zacho believes that the prognosis for primary osteomalacia is good if the condition is treated early. The prognosis for the secondary form depends on the cause of the primary disease; if this is incurable, a constant addition of a surplus of vitamin D and calcium salts may be necessary to prevent recurrence of the bone disease.

[ED. NOTE: It seems important to bring out the significance of vitamin D in relation to senile osteoporosis. Probably the pain, the disability and the deformity that are associated with this disease could be obviated for many patients if patients were given adequate prophylactic doses of vitamin D when they consult the physician for other reasons. The round back deformity of old age, which seems to be common, and the frequent lesions of the spine, such as compression fracture after relatively slight trauma, are probably related to vitamin D deficiency, either to the primary form due to a defect of diet or to the secondary form due to disturbance of absorption, excretion or internal secretion.]

Radicular Syndrome and Referred Pain.—As pointed out by Ussher,⁴²⁴

The existence of radiation phenomena as the result of radiculitis, "intercostal neuritis," and parietal muscle spasm due to disturbances in the region of the

424. Ussher, N. T.: The Viscerospinal Syndrome: A New Concept of Viscero-motor and Sensory Changes in Relation to Deranged Spinal Structures, *Ann. Int. Med.* 13:2057-2090 (May) 1940.

spine, is now generally accepted by clinicians, more particularly by orthopedic surgeons and less universally by the internist. Two chief considerations have been stressed in this "radicular syndrome," viz.: (1) cutaneous hyperesthesia and tenderness in the distribution of the spinal segment involved, and (2) muscle spasm or atrophy of muscle groups in the somatic periphery related to this segment.

He adds a third, a visceral component, and discusses this "viscerospinal syndrome," as he describes "the physiological changes in the viscera produced by essentially the same factors as cause the parietal radiation phenomena." He delineates the pathways involved in "the possible anatomical and physiological connections between the autonomic fibers found in the skin, dorsal musculature and vertebral articulations on the one hand and autonomic fibers innervating the viscera on the other." He groups the different visceral components with the related segmental levels of the nervous system and stresses the importance of this syndrome in the differential diagnosis of visceral disease. He reports more than 400 instances of this syndrome, in at least 40 per cent of which there were multiple manifestations dependent on the various segmental levels involved. He discusses the many symptoms referred to the head, the neck, the chest, the heart, the lungs, the alimentary canal and the genitourinary tract which may be due to stimulation of the skin, the dorsal muscles or vertebral articulations. He gives an explanation for the relief of many visceral symptoms, such as asthma and cardiac and gastrointestinal symptoms, which is said to be obtained by osteopathic treatments or physical therapy and stresses the importance of postural training and physical therapy in the relief of many patients with these visceral disorders.

Rich⁴²⁵ discusses one phase of this so-called radicular syndrome or "viscerospinal syndrome" which he terms "spinal appendicitis." He points out that

it is now becoming more generally recognized that many pains in the body are not due to local or visceral diseases but are referred pains originating from strain, trauma or inflammation in or around the intervertebral foramina. Two regions of the spine are particularly susceptible to strain or injury. They are the dorsi-lumbar, the region of greatest mobility, and the lumbo-sacral, the region carrying the greatest weight. Both areas are situated at the junction of a primary fixed curve with a secondary mobile curve.

The author points out that while "it is generally agreed that sciatica originates in and is referred from the lumbo-sacral region . . . referred pain from the dorsi-lumbar region is not so generally recognized." He states that in older, more rigidly supported spines, the strain will be felt in the lumbosacral region since here there is greater

425. Rich, C. B.: Spinal Appendicitis, *Canad. M. A. J.* **43**:260-264 (Sept.) 1940.

weight, and lessened mobility of the spine as a whole would concentrate the forces of gravity at this point. In most cases, therefore, the patients are middle-aged persons. Rich then described the long lean type of adolescents (in whom appendicitis is common) with poor posture, subjected to unusual fatigue and back strain and frequently introverted, who complain of pain in the right side of the abdomen, which is often confused with pain due to appendicitis. He points out that the differential diagnosis in these cases in which pain is referred from the dorso-lumbar area is aided by the observation that the pain is always relieved by rest, returning on active or passive movement, and that while tenderness and muscle spasm may be present the other signs and symptoms of appendicitis are absent. Huckell⁴²⁶ observes that on "tightening the abdominal muscles, and on palpation, the pain is still present. In intraperitoneal lesions the pain is absent." Rich advises search for foci of infection, training on correct posture, use of supporting belts and avoidance of fatigue and any occupation or movement which involves strain.

Ussher stresses the importance of the skin, the dorsal muscles and the vertebral articulations, and Rich discusses the vertebral bodies with hypertrophic arthritis, the nucleus pulposus, the intervertebral ligaments, the ligamentum flavum, the apophysial joint affected by inflammation and swelling and especially the intervertebral foramina, as the sites of lesions producing referred pain; Goldthwait,⁴²⁷ however, points out the importance of the rib joints as a source of referred pain. He states that the twenty-four costovertebral joints and the twenty costotransverse joints (never entirely at rest unless they become ankylosed) "may become irritated, strained or diseased, with the added possibility of irritation of the nerves adjacent to the joints and pain referred to the distribution of the special nerves." He points out that in the position in which the body is often held the chest sags and the head and shoulders are rounded forward so that the ribs hang below the normal low point of rib function (the neutral position is about 30 degrees downward from the horizontal). He likewise states that

since there is no costotransverse articulation to limit the motion of the main joint, and since the rib is not supported in front by the costosternal cartilage, the floating ribs, two on each side, are able to sag and move about much more, naturally with much greater strain on the rib joint, and with much greater possibility of irritation of the nerve root and trunks. The posterior position that these ribs frequently assume must mean not only a marked backward position of the rib itself, with strain to the joint, but twist of the rib as well. The

426. Huckell, R. G., cited by Rich.⁴²⁵

427. Goldthwait, J. E.: The Rib Joints. *New England J. Med.* **223**:568-573 (Oct. 10) 1940.

referred pain that would come from irritation of the nerve roots adjacent to these ribs is referred to the sides of the abdomen from the pubic bone to the crest of the ilium. . . . Also, since there is a sympathetic ganglion connected with the nerve adjacent to the head of the rib, some of the circulatory disturbances undoubtedly find their explanation in irritation of this ganglion.

[ED. NOTE: These three articles are indicative of the increased interest in the problem of referred pain, especially that from lesions of the spine, and they bring out some important diagnostic points which are probably frequently overlooked. The recent more general use of superficial or deep injection of local anesthetics for various lesions related to the spine will probably add more light to the diagnostic and therapeutic difficulties in the problem of the lesions of the spine. The importance of poor posture as a cause of many symptoms other than backache and fatigue is now more generally appreciated.]

(To be concluded)

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TREATMENT OF HYPOPROTEINEMIA BY ORAL ADMINISTRATION OF PROTEIN HYDROLYSATE

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The importance of proteins in the blood plasma has been demonstrated by numerous investigators. Proteins are normally present in human plasma to the extent of 6.5 to 7.5 Gm. per hundred cubic centimeters with albumin and globulin fractions in the ratio of about 1.6 to 1. In addition to the proteins in the plasma there is also a large store of proteins within the body which can be called on in time of need.

Natural foods contain complex proteins which must be broken down by the digestive enzymes to amino acids and peptides before absorption from the intestines can take place. During disease the digestive processes may not be able to maintain the proteins in the plasma. The store of proteins may also be depleted by rapid loss of plasma from the raw surfaces of burns, by copious drainage of abscesses or of other inflamed cavities or by loss of plasma during prolonged operations on the gastrointestinal tract. A dog may be made hypoproteinemic by repeated plasmapheresis and kept in that state for many months.¹ Although determinations of proteins in the plasma of such an animal show low normal values, the dog is really devoid of all or most of its store of proteins and cannot mobilize proteins if the need arises. Similar depletion of proteins may take place in persons with severe burns, particularly if these are infected or are allowed to weep. Laboratory determinations made four to ten weeks after injury may show low normal values, but these do not indicate the true state of the store of proteins. If grafting operations are then attempted, acute hypoproteinemia may develop, and the grafts may not take. If patients are given adequate replacement therapy, hypoproteinemia is not likely

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1. Madden, S. C., and Whipple, G. H.: *Physiol. Rev.* 20:194-217 (April) 1940.

to develop. Furthermore, there is good evidence that prolonged hypoproteinemia does not materially injure the protein-forming mechanism.²

Plasma proteins and the general protein store can be synthesized by the human body if it receives the proper mixture of amino acids.¹ Ten amino acids—valine, leucine, isoleucine, threonine, arginine, methionine, tryptophan, phenylalanine, histidine and lysine—are considered essential. Cystine also is important. With a mixture of amino acids or of the products synthesized from them, replacement might be accomplished by (1) direct parenteral introduction of the synthesized products in the form of hydrated or dried plasma, (2) parenteral administration of amino acids or (3) oral administration of amino acids or immediate precursors of these with a view to their absorption from the gastrointestinal tract.

The first is a satisfactory and rapid method but has certain disadvantages. Human plasma is not readily obtainable in quantities large enough for building up protein stores, notwithstanding the fact that plasma banks have been established at many centers. About 1,000 cc. of plasma is required to raise the protein content of the plasma of the average adult 1 Gm. per hundred cubic centimeters. In severe hypoproteinemia many liters of plasma may be needed. When plasma is given, absorption and synthesis are unnecessary.

The second method has been employed by Elman,³ Farr and MacFayden,⁴ Shohl and associates,⁵ Whipple and associates⁶ and others. Theoretically the method is good, but it presents several practical difficulties, not the least of which is the preparation of a standardized hydrolysate safe for parenteral use.

It is the third method which interested us. Amino acids are absorbed rapidly from the gastrointestinal tract. Theoretically, therefore, essential amino acids introduced into the upper jejunum should be promptly absorbed. Pure amino acids are not introduced into the intestinal tract in any considerable quantity for several reasons. They are extremely expensive and difficult to obtain in pure form. They are irritating to the upper portion of the normal small intestine if introduced in large quantities.⁷ The further the breaking down of any given protein pro-

2. Madden, S. C.; Noehren, W. A.; Waraich, G. S., and Whipple, G. H.: *J. Exper. Med.* **69**:721-738 (May) 1939. Melnick, D., and Cowgill, G. R.: *ibid.* **66**:493-508 (Oct.) 1937.

3. Elman, R.: *Ann. Surg.* **112**:594-602 (Oct.) 1940.

4. Farr, L. E., and MacFayden, D. A.: *Proc. Soc. Exper. Biol. & Med.* **42**:444-446 (Nov.) 1939.

5. Shohl, A. T.; Butler, A. M.; Blackfan, K. D., and MacLachlan, E.: *J. Pediat.* **15**:469-475 (Oct.) 1939.

6. Madden, S. C.; Zeldis, L. J.; Hengerer, A. D.; Miller, L. L., and Whipple, G. H.: *Science* **93**:330-331 (April 4) 1941.

7. Abbott, W. O.: *Ann. Surg.* **112**:584-593 (Oct.) 1940.

gresses, the more irritating the products become. A compromise may be effected by hydrolyzing certain proteins to the extent that the hydrolysate contains peptides in addition to amino acids. The product we have been using⁸ is an enzymatic hydrolysate of proteins from beef, wheat and milk. From this mixture an adequate amount of each of the essential amino acids is obtained, including methionine, which has recently been shown to have the property of protecting the liver against chloroform and probably against similar anesthetics.⁹

The difficulties in the parenteral use of amino acids and large quantities of human plasma in smaller hospitals led us to investigate the possibility of replacing the store of proteins and proteins in the plasma by administering amino acids and somewhat larger aggregates of protein into the intestinal tract. If rapid replacement could be obtained in this manner, the method of administration would be valuable for persons with severe and extensive burns, for example, even though these persons might not have the benefit of plasma transfusions. Furthermore, if this replacement was reasonably prompt, a minimum of plasma might be employed as an initial emergency measure, to be reenforced by the oral hydrolysate.

All routine determinations of the proteins in the plasma in this study were performed by the falling drop method. We selected this method for several reasons. Hypoproteinemia is only part of the picture in the average case, and the falling drop studies give information regarding the state of hydration without which it is impossible to determine the true level of proteins. The method is accurate and compares well with the salting-out process. It does not indicate the albumin-globulin ratio and gives erroneous information under certain circumstances. The albumin-globulin ratio, however, is seldom necessary except in comparative studies. Then it can be determined by the usual Kjeldahl process. In the presence of gross hemolysis, hyperbilirubinemia, severe diabetes, gross lipemia and hypercholesteremia the falling drop method may give false results. The method depends on the close relationship between the specific gravity of the plasma and the amount of protein present. The lipemia of nephrosis, for example, may alter the specific gravity to such an extent that the falling drop calculations are confusing and unreliable. Hematocrit determination is necessary for interpretation of the plasma protein values. A hypoproteinemic patient may present an apparently normal value because of moderate hemoconcentration. Low protein values are likewise obtained at the end of pregnancy because of hydremia.

8. This preparation, known as aminoids, was supplied for this work by the Arlington Chemical Company.

9. Miller, L. L.; Ross, J. F., and Whipple, G. H.: *Am. J. M. Sc.* **200**:739-756 (Dec.) 1940.

To test whether the protein hydrolysate used causes a rise of protein values when introduced into the gastrointestinal tract, we employed it in treating 30 patients with hypoproteinemia due to various causes. Since the laboratory information in 3 cases was inadequate, those cases were eliminated from the calculations. Table 1 lists the types of patients treated with the hydrolysate. Six cases are briefly reported.

REPORT OF CASES

CASE 1.—A 29 year old white man was admitted on Aug. 20, 1940 in shock after sustaining extensive second and third degree burns on the arms, the back, the buttocks, the thighs, the legs and the feet and first degree burns of the abdomen. After débridement and cleansing, the burns on the trunk were sprayed with tannic acid, and those on the extremities were treated with ethylaminobenzoate ointment.

TABLE 1.—*Patients Treated by Oral Administration of the Protein Hydrolysate*

Primary Complaint	Additional Data	Patients
Carcinoma of the colon.....	Operated on by two stage resection...	1
Carcinoma of the rectum.....	Operated on by one stage resection...	1
Carcinoma of the rectum.....	Operated on by two stage resection...	1
Extensive second and third degree burns..	5
Thrombophlebitis of appendiceal vein....	Infarct of the liver and lung present..	1
Cholecystitis.....	Cholecystectomy performed and continuous suction applied.....	2
Appendiceal abscess.....	Continuous suction applied.....	1
Pyelitis of pregnancy.....	2
Ruptured ectopic pregnancy.....	1
Rectal polyps.....	Hemorrhage occurred repeatedly.....	1
Papillary cystadenoma of ovary.....	Operation performed	1
Strangulated hernia.....	1
Obstruction of the liver.....	2
Nutritional hypoproteinemia, allergy and dermatitis.....	2
Perforated peptic ulcer.....	Continuous suction applied.....	1
Acute glomerulonephritis.....	3
Lacerations of the cervix.....	Hemorrhage occurred repeatedly.....	1

Shock was controlled with elevation of the foot of the bed, heat, 10 cc. of an extract of adrenal cortex and 1,000 cc. of a 5 per cent solution of dextrose in physiologic solution of sodium chloride, given intravenously. The protein hydrolysate was given the same evening. With treatment, as shown in chart 1, his condition was good on the sixteenth day. One day later staphylococcic cellulitis developed in his right groin; this was controlled with sulfathiazole (2-[para-aminobenzenesulfonamido]-thiazole). A rapid drop of proteins in the plasma occurred but this was corrected by oral feeding of the protein hydrolysate. No plasma or whole blood was given.

CASE 2.—A 23 year old white man was injured in the same accident as the patient in case 1. He was admitted in intense pain with third degree burns of the left hand, the forearm, the arm and the shoulder, second and third degree burns of the left side of the thorax and the abdomen, second degree burns of the right hand and the forearm, and first degree burns of the penis, the scrotum, the perineum and the thighs. The burned areas were thoroughly cleaned, débrided and treated with tannic acid spray. The foot of the bed was elevated; warmth was applied, and the patient was given 2,000 cc. of a 5 per cent solution of dextrose in physiologic solution of sodium chloride and 10 cc. of an extract of adrenal

cortex intravenously. He remained in shock for many hours, but within thirty-six hours the hematocrit determination was reduced from 64 to 59 per cent. The protein hydrolysate was given orally, and the plasma proteins gradually rose, as shown in chart 2. He became ambulatory on the thirty-seventh day and later had two successful grafting operations without compromising the plasma protein values. No plasma or whole blood was given.

CASE 3.—A Negro boy 8 months old was admitted on July 6, 1940 and discharged improved to the clinic on October 3. Three weeks prior to admission his legs and feet became swollen. The swelling gradually spread over the entire body and was accompanied by a generalized maculopapular erythematous rash.

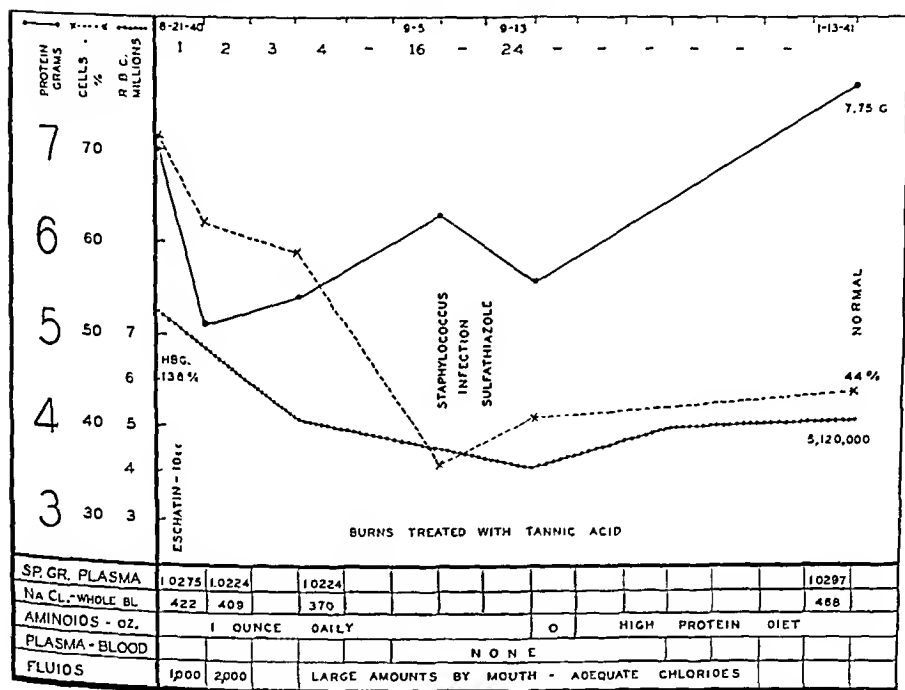


Chart 1.—Treatment and course of patient in case 1, a 29 year old man.

He took breast milk twice daily but was unable to retain cow's milk. On admission he had generalized edema with pitting on pressure, in addition to the rash. The abdomen was distended and contained much fluid. Since the urine failed to show evidence of nephritis and the proteins in the plasma amounted to 2.83 Gm. per hundred cubic centimeters, a diagnosis of nutritional edema, hypoproteinemia and allergy was made. Various diets failed to raise the proteins above 2.90 Gm., and on July 22 oral administration of the hydrolysate was started. Within eight days on a dosage of 2 drachms (7.76 Gm.) daily, the child gained weight, the plasma proteins rose to 5.08 Gm. per hundred cubic centimeters and the rash lessened. Both the rash and the edema had disappeared on the fifteenth day. Ingestion of carrots brought about a return of the rash. The patient's condition was excellent up to the twenty-ninth day when administration of the hydrolysate

was discontinued. The child had also received 15 ounces (443.5 cc.) of corn syrup (Karo) and goat's milk daily. These were insufficient to maintain a stationary level of protein in the plasma. On the fifty-first day edema was again present, accompanied by a rash. The protein hydrolysate was given daily in a dose of 4 drachms (15.5 Gm.). The proteins in the plasma rose rapidly; the edema disappeared; the child gained weight, and his condition became good. Skin tests showed that he was sensitive to cow's milk, dust and several vegetables. Elimination diets indicated sensitivity to carrots and a number of other foods. Smears of his blood repeatedly showed a large percentage of eosinophils, up to 28. At the time of writing the child comes to the clinic and is in excellent condition, with plasma protein values well toward the upper limits of normal. He still takes the protein hydrolysate regularly. Data on this case are presented in chart 3.

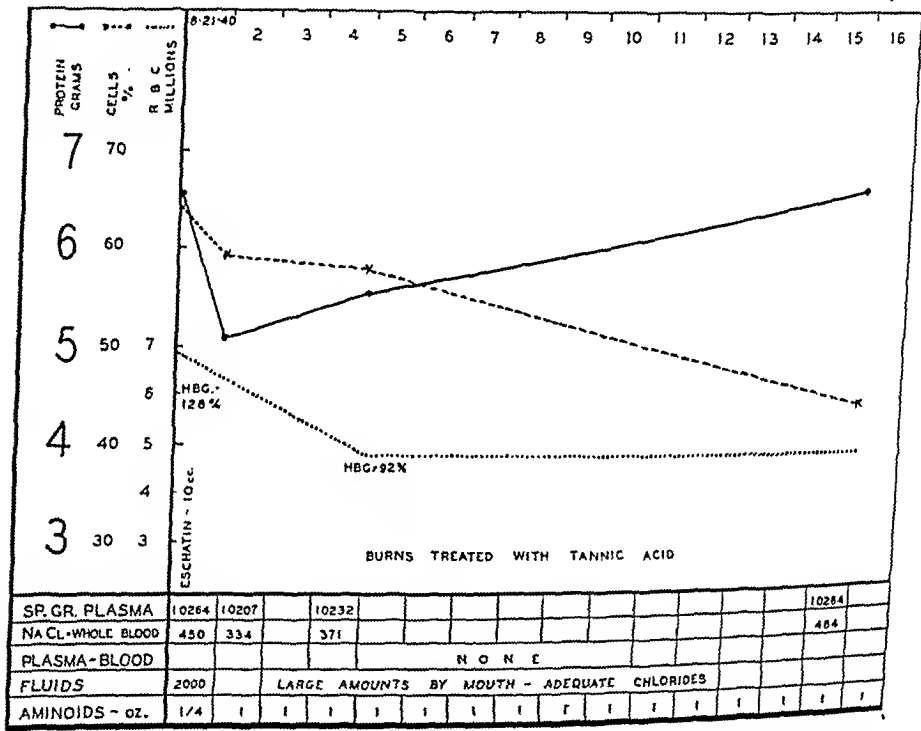


Chart 2.—Treatment and course of patient in case 2, a 23 year old man.

CASE 4.—An acutely ill and debilitated white man 31 years old was admitted to the hospital on Nov. 19, 1940 for a plastic operation over burns sustained seven weeks before. All mucosal surfaces were dehydrated. He had large denuded granulating surfaces on his left side from third degree burns of the hand, the forearm, the arm, the thorax, the abdomen, the thigh and the leg. On the day after admission the hematocrit determination showed 46 per cent cells; the proteins in the plasma amounted to 5.27 Gm. per hundred cubic centimeters. When grafts were applied five days later he went into profound shock, from which he was retrieved with difficulty. Two days later the proteins in the plasma were down to 4.66 Gm.; after 1,000 cc. of whole blood was given, they were 5.09 Gm. After three days of dosage with 1½ ounces (44.35 cc.) of the protein hydrolysate daily, the proteins rose to 5.95 Gm. One week later he tolerated a grafting operation. He received 2,000 cc. of whole blood over a period of two months and had four

more operations. He stood these well, and his plasma proteins gradually increased to 7.38 Gm. All later grafts were successful.

CASE 5.—A Negro woman 47 years old was admitted on Nov. 14, 1940 with a history of obstipation for three days and a diagnosis of acute intestinal obstruction. At operation on November 16 the distention was found to be confined to the cecum and the ascending colon. A cecostomy was performed after an annular obstructing growth in the sigmoid colon had been located. After the operation she was given 3 ounces (88.5 cc.) of the protein hydrolysate daily by mouth, and the proteins in the plasma rose promptly (chart 4) to 7.8 Gm. per hundred cubic centimeters on December 14, when the administration of the hydrolysate was discontinued. During a stormy postoperative course atelectasis developed. On

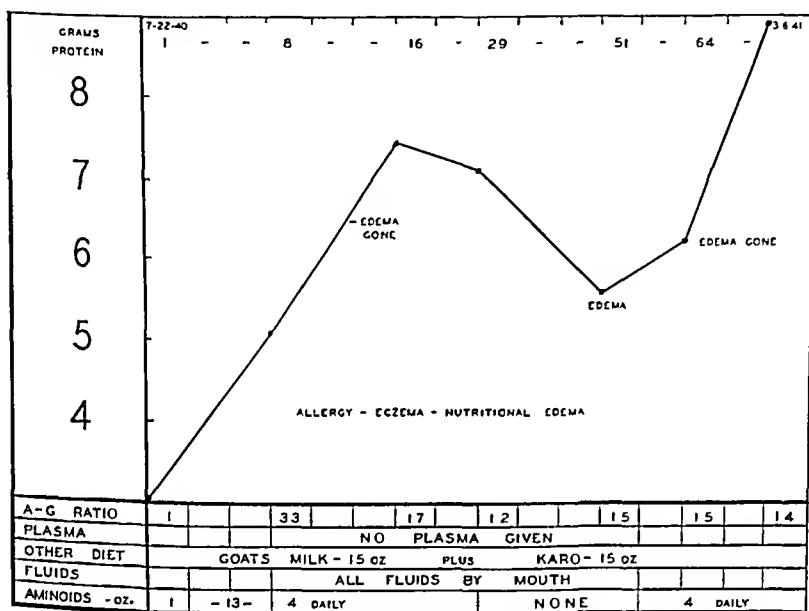


Chart 3.—Treatment and course of patient in case 3, a male child 8 months old.

Jan. 16, 1941 the growth in the sigmoid colon was exteriorized by a Mikulicz operation. The proteins in the plasma dropped rapidly and four days later were 5.6 Gm. With daily administration of 3 ounces (88.5 cc.) of the protein hydrolysate the protein values became 6.8 Gm. on the day of the last operation for closure of the original cecostomy.

CASE 6.—On March 4, 1940 cholecystectomy was performed on a 51 year old white woman with cholelithiasis. Ileus developed, and the operating surgeon performed an ileostomy on March 22. Her condition was thenceforth extremely grave, and transfusions failed to maintain the proteins in the plasma within normal limits. On April 19 the value of proteins was 5.44 Gm. per hundred cubic centimeters. On April 22 the ileostomy was closed, and on April 24 a transfusion of 800 cc. of whole blood was given. Administration of the protein hydrolysate was started, ½ ounce (14.5 cc.) three times daily, because of a further drop of

the proteins to 4.93 Gm. On April 26 the value of proteins in the plasma was 4.76 Gm. and on April 27, 5.37 Gm. The proteins had increased to 6.25 Gm. on May 3. When the proteins were low, the bowel, the skin and the subcutaneous tissues were edematous. Restoration of the plasma protein levels to normal with the hydrolysate promptly eliminated the edema.

COMMENT

Many of the interesting features of the cases presented were observed in other cases of the series. Case 3 is instructive because of the profound hypoproteinemia and the inability of the patient to tolerate ordinary

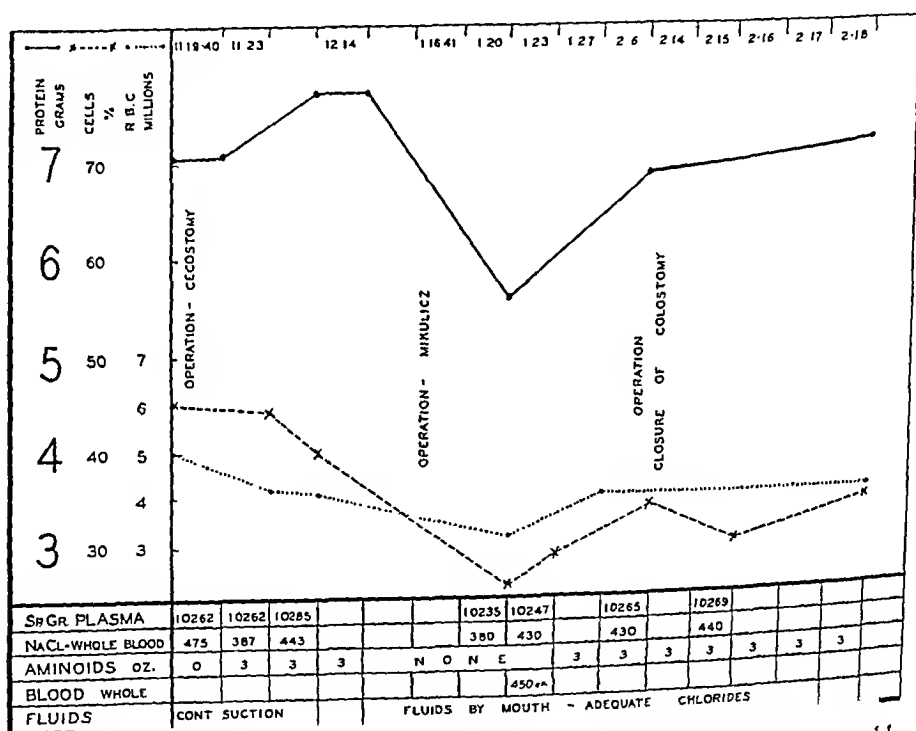


Chart 4.—Treatment and course of patient in case 5, a woman 47 years old.

forms of nourishment. With the daily administration of 2 drachms (7.5 Gm.) of the protein hydrolysate daily (about 0.75 drachm per 10 pounds [3 Gm. per 4.5 Kg.] of body weight) the proteins in the plasma were increased from 2.9 to 5.08 Gm. per hundred cubic centimeters in one week; the average daily increment was thus 0.3 Gm. At the same rate, the proteins in the plasma rose to 7.40 Gm. at the end of fifteen days. The child received corn syrup and goat's milk alone from the twenty-ninth to the fifty-first day, but the proteins fell steadily until edema reappeared a little before they reached a level of 5.6 Gm. The resumption of the protein hydrolysate feeding promptly corrected the condition for the second time, demonstrating that the rise was due to the hydrolysate. On March 6 the proteins in the plasma reached the high

level of 8.89 Gm. The child was never able to take enough of the goat's milk to maintain his weight or his plasma protein levels.

Cases 4 and 5 illustrate the danger of operating on persons whose store of proteins has become depleted and also typify two major causes of hypoproteinemia in patients who have had operations. When depletion of proteins is as severe as in case 4, the level of proteins in the plasma tends to be below normal. Unfortunately, a reduced store of proteins is not always accompanied by a low level of proteins in the plasma. The extent of depletion may not become evident until mobilization is required; then acute hypoproteinemia develops. Such a demand is made during and after an operation on the gastrointestinal tract. The protein hydrolysate should, therefore, be given orally during the preoperative and the postoperative period. During the latter period the mixture may be given through an indwelling double-barreled tube into the duodenum or the jejunum. This permits maintenance of levels of proteins and prompt healing of wounds in the intestine and the abdomen and prevents the mechanical difficulties resulting from hypoproteinemic edema. Case 5 demonstrates that it is not enough merely to raise the level of proteins in the plasma to normal. Dosage of the protein hydrolysate must be continued to build up the reserve stores; had that been done in this case the upper line on chart 4 would not dip down between the first two operations. Both cases show that the protein hydrolysate maintains satisfactory levels during and after operation. However, this was not accomplished in either case until the hydrolysate therapy was instituted.

Case 6 offers an excellent example of the pitfalls which may trap the unwary in operations on the intestine. Hypoproteinemia will develop rapidly during the period after operation. It develops mainly from three causes: the more or less prolonged malnutrition prior to operation, the loss of plasma during operation and the lack of nutriment from four to seven days after operation. The postoperative course may be complicated by drainage and continuous or interrupted suction through an indwelling tube into the duodenum or the jejunum. A patient may be able to cope with any one of these factors successfully, but he may have trouble if two are present. He surely will have trouble if all three occur, for then the usual concomitants or hypoproteinemia appear. The intestines become edematous, particularly in traumatized areas such as the suture lines; stomas from gastroenterostomy and other anastomoses become obstructed by edema; healing ceases, and a grave state of affairs comes to exist. We think that the seriousness of the situation is greatly increased if the surgeon has not properly introduced a suitable double-barreled tube well through the anastomosis into the jejunum or the duodenum as the case requires. It is then impossible to get any nutriment or fluid past the stomach. Jejunostomies performed at this time

will be worthless. The only way out is to give sufficient plasma intravenously to raise the proteins in the plasma to nearly normal levels and to be careful not to give more sodium chloride than is required. Intravenous administration of amino acids may also be indicated and may be employed if the difficulties in preparation and the dangers in use are eliminated. If the indwelling tube has been properly placed during operation, the protein hydrolysate may be introduced directly into the duodenum or the jejunum. We have successfully given the hydrolysate by this method, thereby maintaining satisfactory levels of proteins in the plasma.

To compare the results in the various cases of the series it was necessary to eliminate some of the factors which tend to make the plasma protein values incomparable. All plasma protein values were therefore corrected to conform with an ideal erythrocyte count of 4,500,000 cells and an ideal hematocrit determination of 45 per cent cells. Thus variations in blood concentration and cell counts were eliminated. Analysis of the figures obtained revealed that with few exceptions the highest daily rate of increase tended to occur during the first seven days of therapy and that the daily rate from the seventh to the twenty-sixth day seemed to decrease materially. In several cases a steady rate was maintained, and in 1 case there was actually an increase after seven days. These were exceptions. Because of these tendencies the series was first analyzed as a whole and then in two portions, the dividing line being placed at the end of the seventh day. The mean daily rise of protein in the plasma in 25 cases was 0.147 Gm., with a standard deviation of 0.1225 Gm., which shows a wide distribution about the mean value. The maximum daily rise was 0.51 Gm.; the minimum, 0.01 Gm. (chart 5). The mean daily rise during the first seven days was 0.2 Gm. with a standard deviation of 0.1228, which shows less wide distribution. The mean daily rise between the end of the seventh day and the twenty-sixth day was 0.092 Gm., less than half the rate of the first period. The standard deviation of the difference of 0.1078 between the means of the two periods was 0.0135, which indicates that the difference is probably significant. Likewise, the difference of 0.053 between the means of the entire series and of the first period had a standard deviation of 0.0117. If the 3 cases of glomerulonephritis and the 2 cases of cirrhosis of the liver are eliminated from the calculations, the results are much more striking.

Cases 1 and 2 are dealt with separately because of the complicating factors of shock and excessive hemoconcentration. The patients were treated by oral administration of the protein hydrolysate, without any plasma or whole blood. From the corrected values it will be seen that the proteins in the plasma decreased during the first seventy-two hours and afterward rose rapidly. The proteins continued to decrease for forty-eight hours after the hydrolysate therapy had been started. In

other words, it took three days for sufficient proteins to be assimilated and for the burned surfaces to be brought into sufficient control to eliminate the excessive loss of plasma. Probably this drop would not have been so prolonged if the loss of plasma had ceased promptly during the first twenty-four hours. At any rate, the administration of several thousand cubic centimeters of plasma would have prevented acute hypoproteinemia and would have greatly lessened the period of shock in each case. The protein hydrolysate taken by mouth does not appear to be adequate for alleviating shock and the accompanying acute hypoproteinemia; the oral administration of the hydrolysate should be simultaneous with an intravenous injection of plasma to reenforce the proteins and

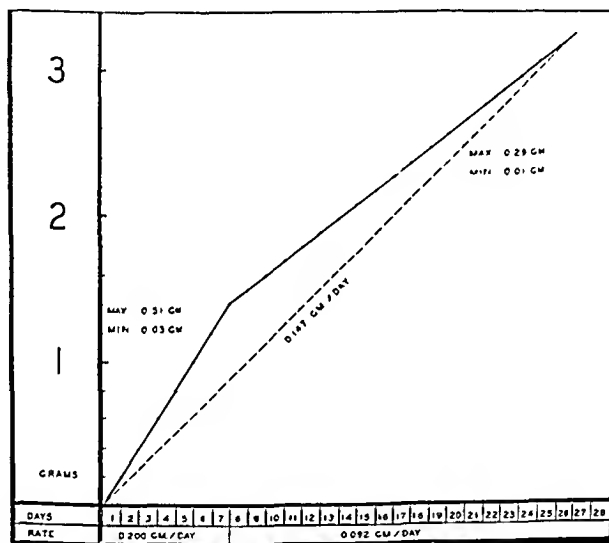


Chart 5.—Mean daily increase of proteins in the blood plasma of 25 patients treated with 1½ ounces (44.5 cc.) of the protein hydrolysate daily.

take care of the needs after the first twenty-four hours. Chart 6 depicts graphically the progress in these 2 cases.

From the oral administration of protein we have observed replenishment of the body's store of proteins, elevation of the levels of proteins in the plasma and gain in weight. One must conclude that administration of any hydrolysate of protein containing the essential amino acids and polypeptides with cystine will probably produce the same results. Furthermore, such a hydrolysate could be prepared in the hospital from readily obtainable foodstuffs. The production of a protein digest by enzymatic means is troublesome, expensive and beyond the reach of the staff of the ordinary hospital. A uniform preparation, constant in composition, readily obtainable and miscible and made up of the essential

amino acids and polypeptides would be advantageous. A diet with adequate amounts of proteins will result in replenishment of protein stores and plasma proteins. This replenishment will be much slower and will depend on the ability of the digestive tract to deal with the complex molecules of proteins. A hydrolysate is more easily dealt with.

While subcutaneous injection of amino acids and polypeptides, as recently reported,⁶ appears reasonably safe, with no reactions to the preparation used, intravenous administration seems more hazardous. The authors state that an enzymatic digest of commercial casein given parenterally is as effective as whole liver given by mouth. Whether the effectiveness is greater than that of a protein hydrolysate given by mouth or through an indwelling tube cannot be stated at this time. Although

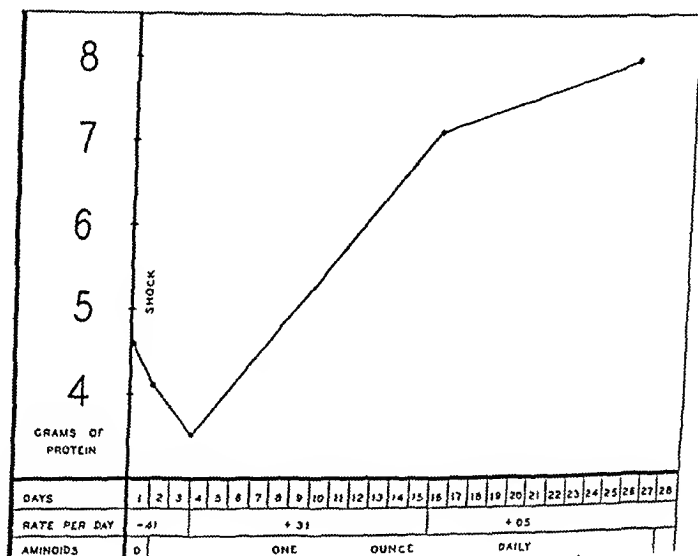


Chart 6.—Curve of average values of proteins in the plasma of patients in cases 1 and 2 after correction.

large amounts of a hydrolysate may be irritating, it is possible to give a 25 per cent solution in physiologic solution of sodium chloride or water as a slow continuous drip through an indwelling tube. Thus large amounts may be given in twenty-four hours. We have not made a sufficient study of this method to state the mean increase of plasma protein following employment of this method. The continuous drip administration is simple and requires no more than the ordinary set for administering fluids intravenously. There should be a drip chamber in the line for adjustment of the rate of flow. The 25 per cent solution of the hydrolysate is poured into the flask and the drip adjusted to a flow of about 80 drops per minute. This flow is satisfactory, and only occasionally is it necessary to flush the tube with physiologic solution of sodium chloride or water.

SUMMARY

Methods of replacement or restoration of the proteins in the plasma and the body's general store of proteins are discussed with special reference to oral feedings of a protein hydrolysate. A hydrolysate of proteins from beef, milk and wheat was employed in 30 cases for feeding by mouth or through an indwelling tube. It produced satisfactory replacement of proteins in the plasma and correction of the various anomalies which accompany hypoproteinemia. The speed of replacement was rapid but not fast enough for the treatment of shock and immediate hypoproteinemia. The hydrolysate is valuable as an adjunct to intravenously administered plasma.

Six illustrative cases are described.

The preoperative and postoperative use of such a protein hydrolysate in gastrointestinal surgical procedures is important to correct hypoproteinemia before operation and to prevent its occurrence after operation.

The protein hydrolysate, given by an indwelling tube in the duodenum or the jejunum, was well tolerated. Continuous drip feedings of a 25 per cent solution of the hydrolysate were employed. The method is described.

REGIONAL LYMPHATIC METASTASES OF CARCINOMA OF THE STOMACH

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The low incidence of five year cures after partial gastric resection for carcinoma of the stomach is discouraging. However, it is easily explained by the insidiousness of the disease in its early stages; by the time the symptoms become sufficiently alarming to make the patient seek medical aid, the condition is often inoperable. The elimination of certain factors to be discussed later should increase the number of five year cures.

This study, similar to one we made of the regional lymphatic metastases of carcinoma of the rectum¹ and colon,² is based on the dissection and examination of all the regional lymph nodes in 53 cases of carcinoma of the stomach. Fifty-one of the patients had previous partial to subtotal gastric resection, and 2 came to autopsy. The lymph nodes were dissected from each specimen after they had been visualized (fig. 1) by clearing by the Gilchrist and David modification of the Spalteholz method.³ Each node was examined individually and the results charted on diagrammatic drawings. The presence or absence of metastases in regional lymph nodes was then correlated with (1) the age of the patient, (2) the duration of symptoms, (3) the location of the neoplasm within the stomach, (4) the size, (5) the gross type of neoplasm, (6) the depth of infiltration, (7) the degree of cellular dif-

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1. Coller, F. A.; Kay, E. B., and McIntyre, R. S.: Regional Lymphatic Metastases of Carcinoma of the Rectum, *Surgery* 8:294 (Aug.) 1940.
2. Coller, F. A.; Kay, E. B., and McIntyre, R. S.: Regional Lymphatic Metastases of Carcinoma of the Colon, *Ann. Surg.* 114:56 (July) 1941.
3. Gilchrist, R. K., and David, V. C.: Lymphatic Spread of Carcinoma of the Rectum, *Ann. Surg.* 108:621, 1938.

ferentiation and (8) the microscopic type. Regional lymph nodes were thus isolated which go unnoticed by the usual method of dissection. Many large nodes were inflammatory, and many small impalpable nodes contained neoplasm. Unless a lymph node was definitely replaced by carcinoma, it was impossible to determine without microscopic section whether it was involved. Operative procedure should not be minimized because of the absence of palpable lymph nodes.

As a result of this special method of investigation, metastases in regional lymph nodes were observed in 40 of the 53 specimens (75.5 per cent). An average of 30.2 lymph nodes per specimen were isolated. There were 32.8 nodes isolated per specimen in the group having positive regional involvement, compared with 22.4 nodes per specimen

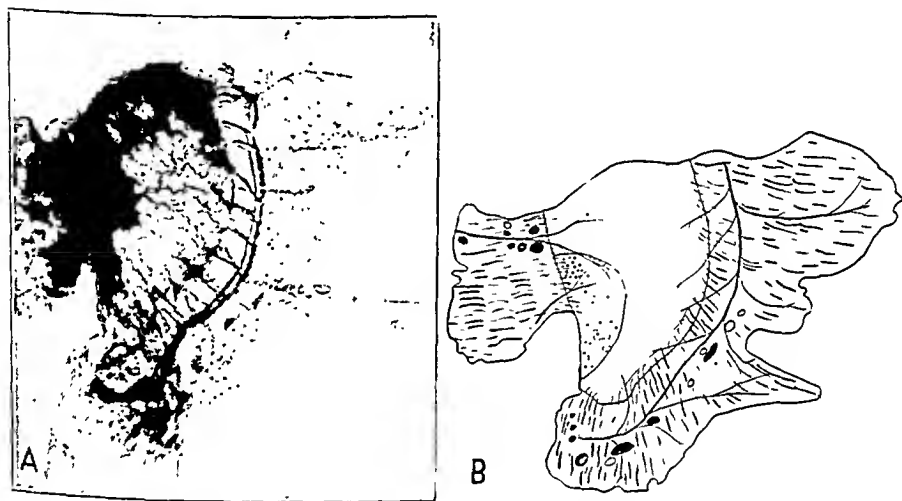


Fig. 1.—*A*, photograph of a cleared specimen. *B*, line drawing of the lymphatic metastases in *A*. Of the 19 lymph nodes isolated, 13 were found to contain microscopic nests of metastatic carcinoma even though not suggestive of metastases grossly.

in the group having no metastases in regional lymph nodes. The largest number of nodes isolated in any one operative specimen was 92, and 14 of these showed evidence of metastatic carcinoma. Of the 13 specimens showing no metastases in lymph nodes, 7 had 13 or less lymph nodes isolated per specimen. Most of the operations in this series were palliative because of extensive local infiltration or poor operative risk (age), and only small segments of the adjacent mesenteries with their included lymph nodes were resected. It is safe to assume that if more of the adjacent supportive tissues had been resected and examined for lymph nodes, involvement of regional lymph nodes

would more closely approximate 88 per cent in this series. Only 6 of the 53 cases (11.2 per cent) were represented by enough lymph nodes to indicate that there were probably no metastases in the regional lymph nodes. Carcinomatous invasion of the submucosal lymph channels of the stomach was present in several of these cases.

For comparison, 55 cases of partial gastric resection for carcinoma, done in 1937 and 1938, were reviewed. The operative specimens had been examined for lymph nodes by gross manual dissection. In 18 of the 55 cases, either lymph nodes were not detected by palpation or, if present, were not thought to be sufficiently suggestive of malignancy to warrant microscopic section, and in only 27 of the 55 cases (49 per cent) was there evidence of metastasis to the regional lymph nodes.

Metastasis to regional lymph nodes is only one factor to be considered in determining the operability and prognosis of carcinoma of the stomach. Inoperability or poor outlook may result from an extensive local infiltration, hematogenic metastases or peritoneal implants. In 15 per cent of the most favorable of the cases in which a partial or subtotal gastric resection was performed, there was microscopic evidence of infiltration into blood vessels, even though gross metastases could not be detected; this was comparable to the 15 per cent microscopic infiltration of blood vessels noted in our study of carcinoma of the rectum. In 47 (88.6 per cent) of the cases the carcinoma had infiltrated completely through the gastric wall and had involved the serosa. This is a constant source of free peritoneal implantation.

The duodenum was involved by the carcinoma in 14 cases (26.4 per cent); in some, by direct extension; in others, through the submucosal and intermuscular lymphatic channels. Careful study of the operative specimens, both the gross specimens and multiple microscopic sections, revealed that in 13 (24.5 per cent) the neoplasm had extended to the upper margin of the resection, usually along the lesser curvature or the posterior wall of the stomach, even though it was impossible to determine this by palpation at the time of operation. It is often difficult to determine by palpation alone the extent of the neoplasm, especially a sessile neoplasm. In this clinic the specimens are now examined grossly as soon as removed, and if any question arises as to the margin of safety, further resection is done.

THE LYMPHATIC DRAINAGE OF THE STOMACH

There are three systems of lymphatics of the stomach: the intramural, the intermediary and the extramural.

Intramural System.—This consists of three networks: the submucosal, the intermuscular and the subserosal. The submucosal lymphatic channels communicate freely with similar channels throughout

the submucosa of the stomach and to a lesser degree with those of the duodenum. They also connect freely with the deeper intermuscular network through radial lymph channels. The intermuscular network is located between the oblique, circular and longitudinal muscle layers. This network communicates with other similar channels as well as draining into the subserosal network found beneath the serosal investment of the stomach.

Intermediary System.—This is made up of numerous small lymph channels between the subserosal network and the extramural collecting systems.

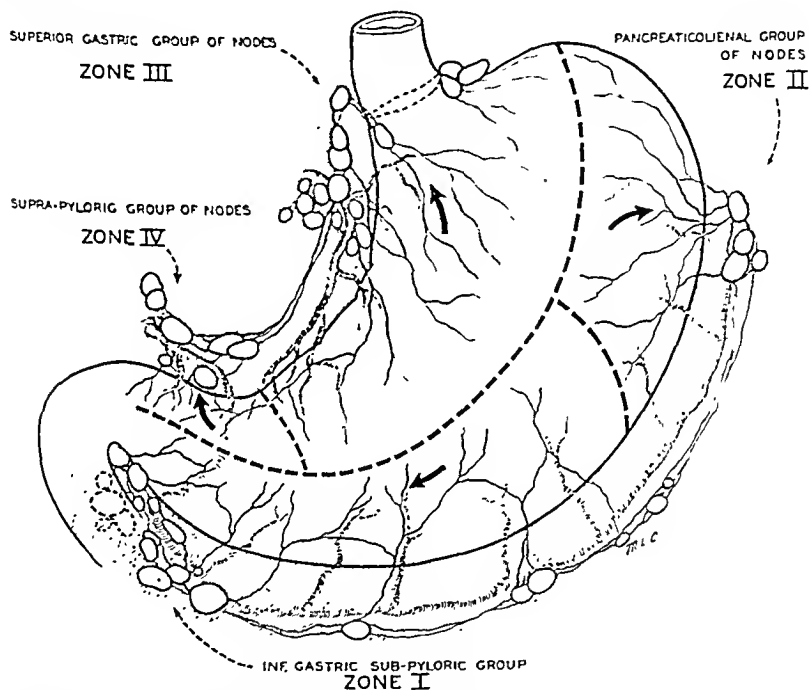


Fig. 2.—Diagrammatic drawing illustrating the zonal lymphatic metastases of carcinoma of the stomach.

Extramural System.—This is comprised of four zones of lymphatic drainage, corresponding largely with the vascular supply of the stomach (fig. 2).

The first zone is the inferior gastric-subpyloric, consisting of a group of nodes and lymphatic channels located in the gastrocolic ligament both above and below the right gastroepiploic vessels. This zone drains the lymph from the pyloric half of the greater curvature of the stomach. The direction of lymph flow is from above downward toward the pylorus and between the head of the pancreas and the second

portion of the duodenum. These lymph channels and nodes accompany the gastroduodenal vessels and eventually drain into the hepatic nodes along the hepatic vessels and into the celiac and aortic nodes. The majority of the nodes in this zone are on the outer aspect of the gastroepiploic vessels, often as much as 3 to 4 cm. from the greater curvature of the stomach. Consequently, any radical removal of these glands must include wide portions of the gastrocolic and duodenocolic ligaments. Residual carcinoma is often left in this zone.

The second zone, or the pancreaticolienal group of glands, is less important, as carcinoma of the stomach in the majority of cases is located in the pyloric antrum and distal one third. However, when it is in the body of the stomach or when the lymph channels of the inferior gastric-subpyloric group are plugged, retrograde metastasis may take place in this zone. This group of nodes and lymphatic channels drains the upper aspect of the cardia and fundus and are found in the gastrocolic and gastrolienal ligaments along the course of the left gastroepiploic vessels. From here their efferent channels drain into the nodes along the splenic vessels lying along the superior aspect of the pancreas. Lymph nodes along the short gastric vessels in the gastropancreatic ligament are occasionally the site of metastases. The efferent channels from the pancreatic nodes drain into the celiac and aortic nodes.

The third zone of lymphatic spread comprises the superior gastric lymph nodes and channels in the lesser omentum following the left gastric artery along the upper two thirds of the lesser curvature. This zone drains the lymph from the lesser curvature half of the stomach except for a small area above the pylorus and the esophageal aspect of the fundus. These nodes are not exactly in the lesser omentum or gastrohepatic ligament but are actually in the ligament containing the left gastric artery which extends from the lesser curvature to the posterior abdominal wall at the celiac axis and above. However, this ligament for the most part is fused with the gastrohepatic ligament, at least at its beginning, and they are usually considered as one. The efferent channels from these nodes for the most part drain to the celiac nodes. The nodes about the cardiac orifice drain somewhat to the esophageal nodes.

The fourth zone includes the suprapyloric nodes, which drain the lymph from the pylorus and the small portion of the lesser curvature of the stomach. The efferent channels of these nodes drain to the hepatic nodes along the hepatic artery and here, in turn, to the celiac and aortic nodes.

Cancer emboli may metastasize in any one or all four zones of lymphatic spread. This fact is beautifully demonstrated by an autopsy specimen in which all the upper abdominal structures about the stomach

were removed, cleared and carefully dissected (fig. 3). The two most important zones of spread appear to be the inferior gastric-subpyloric zone and the superior gastric zone. These are often inadequately excised, because the neoplasm is so extensive that only a palliative procedure is attempted, there are no nodes palpable, or the surgeon is not making a conscientious attempt at complete eradication of the carcinoma. Radical operation for carcinoma of the stomach is different from that for carcinoma in other locations. Many times it is technically impossible to remove much of the adjacent mesentery and ligaments, but extensive

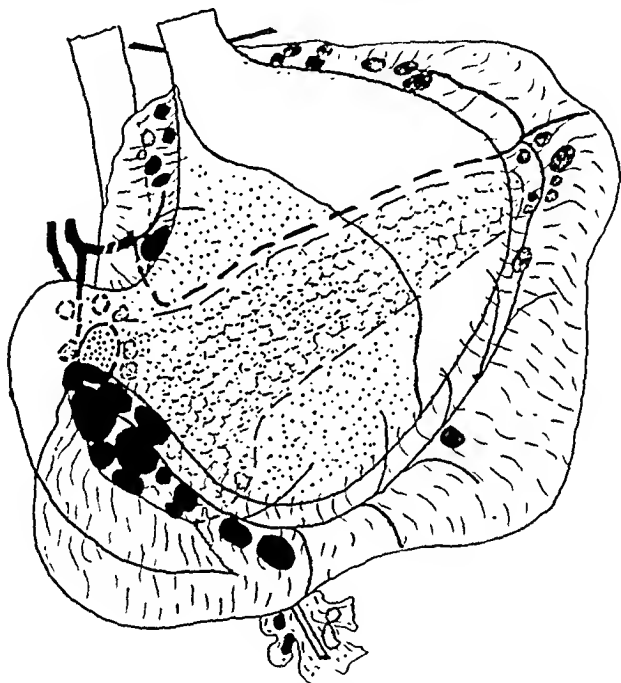


Fig. 3.—Line drawing of an autopsy specimen of carcinoma of the stomach, demonstrating the zonal lymphatic metastases. The extensive nodal metastases to the inferior gastric-subpyloric zone (zone 1) are noted.

removal of as much of the adjacent gland-bearing supportive tissue as possible when the carcinoma is in the early stage and the prognosis favorable is advocated, even though there are no palpable nodes.

Lymphatic vessels differ from blood vessels in that instead of one or two channels draining the same area, the lymph is returned by a number of channels, which tend to form a plexus about the blood vessels. There may also be a number of efferent vessels for any one node; this explains the observation that contiguous lymph nodes may

not be involved. Lymph nodes act as barriers to filter out neoplastic emboli. A neoplastic embolus enters a lymph node by the pericapsular and subcapsular lymph channels. If the metastasis remains viable, it sets up a new neoplastic focus, which tends to block the lymph channel, which then becomes dilated and distended with lymphocytes. The lymph flow becomes static, and other neoplastic foci are often established along the course of the lymph channels. It is therefore quite common to find multiple neoplastic nodules in both the greater and the lesser omentum. The direction of lymph flow determines the direction of lymphatic metastasis. If the lymph channels become plugged with

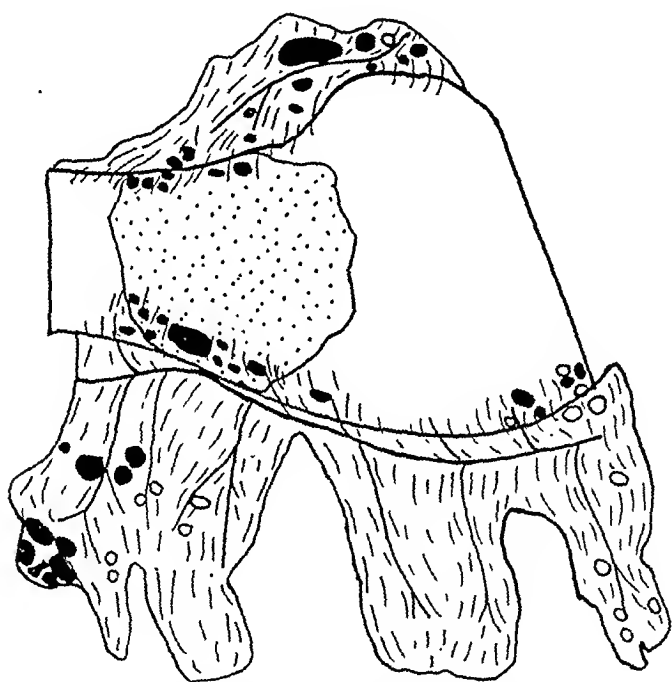


Fig. 4.—Line drawing demonstrating extensive lymphatic metastases of a carcinoma of the stomach after a partial gastric resection.

neoplastic emboli, the lymph will find unobstructed channels, and neoplastic emboli may flow to other zones of the lymphatic spread. In several instances of carcinoma of the pyloric antrum with extensive regional metastasis to the inferior gastric-subpyloric glands, spread to the pancreaticolienal zone took place (fig. 4). The demonstrable zonal distribution in the 40 cases in which there was involvement of regional lymph nodes was as follows: In 34 cases there was lymphatic metastasis to the inferior gastric-subpyloric zone; in 23, to the superior gastric zone; in 12, to the suprapyloric zone; in 7, to the pancreaticolienal zone.

In 5 cases there were four zones of spread; in 4, three zones; in 15, two zones, and in 16, one zone. Of the 34 cases in which there were

metastases to the inferior gastric-subpyloric group, there was involvement of lymph nodes up to the line of resection of the duodenocolic ligament in 21.

In 3 autopsies after partial gastric resection, all the remaining gland-bearing tissues in the four zones of spread were cleared and examined for lymph nodes. In 2 of these, involved nodes were found about the head of the pancreas and the duodenal stump, that is, in zone 1, the inferior gastric-subpyloric zone (figs. 5 and 6).

Fifteen of the 23 cases in which there was metastasis to the regional lymph nodes of the superior gastric zone disclosed involved lymph nodes up to the margin of the excision of the lesser omentum. An insufficient amount of supportive tissue to include any lymph glands was removed

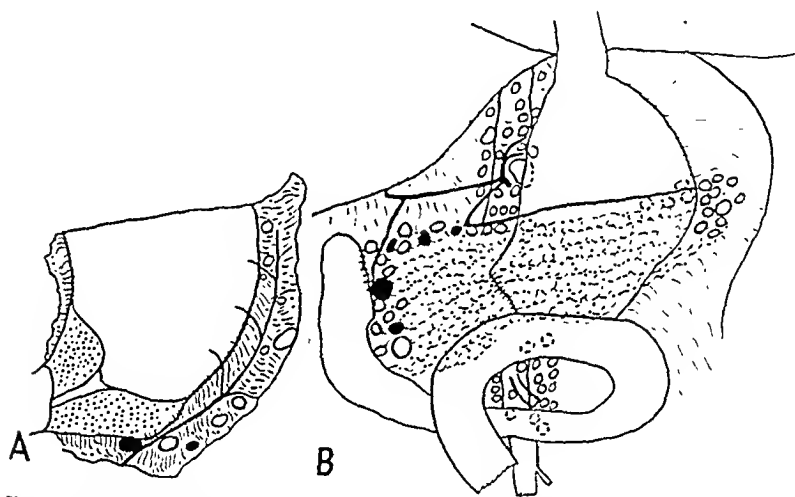


Fig. 5.—*A*, line drawing of the lymphatic metastases of a carcinoma of the stomach, demonstrating the nodal metastases to two lymph nodes in the inferior gastric-subpyloric zone (zone 1) which were close to the line of resection of the gastroduodenal ligament. *B*, line drawing of the residual lymphatic metastases in the inferior gastric-subpyloric zone in the autopsy specimen in the same case. Note that there were 5 lymph nodes about the duodenal stump and head of the pancreas (zone 1) that contained residual carcinoma.

along the lesser curvature in 6 cases. Three of these cases were included in the group in which there were no lymph node metastases. Figure 7 illustrates the type of operation that will probably be associated with the largest number of cures and the smallest operative mortality. The entire omentum was removed from this specimen. The duodenocolic ligament was adequately dissected along the duodenum and head of the pancreas, and by this means the one and only involved lymph node was included. The dissection should be carried well posterior on the lesser curvature to include all of the nodes about the left gastric vessels.

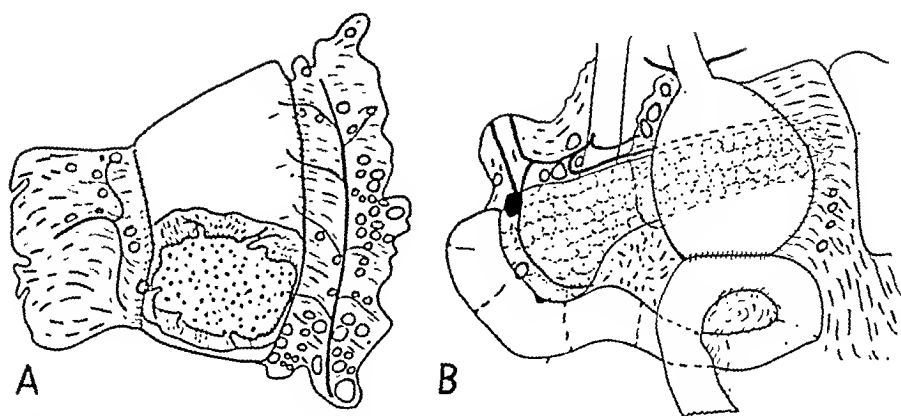


Fig. 6.—*A*, line drawing of the operative specimen in a case of carcinoma of the stomach, demonstrating the absence of nodal metastases even though as many as 60 lymph nodes were isolated. *B*, line drawing of the residual lymphatic metastasis in the inferior gastric-subpyloric zone in the autopsy specimen in the same case. Even though all the susceptible gland-bearing area was thought to have been removed at the time of operation, further examination of the autopsy specimen revealed a single residual metastasis in a lymph node adjacent to the duodenal stump.

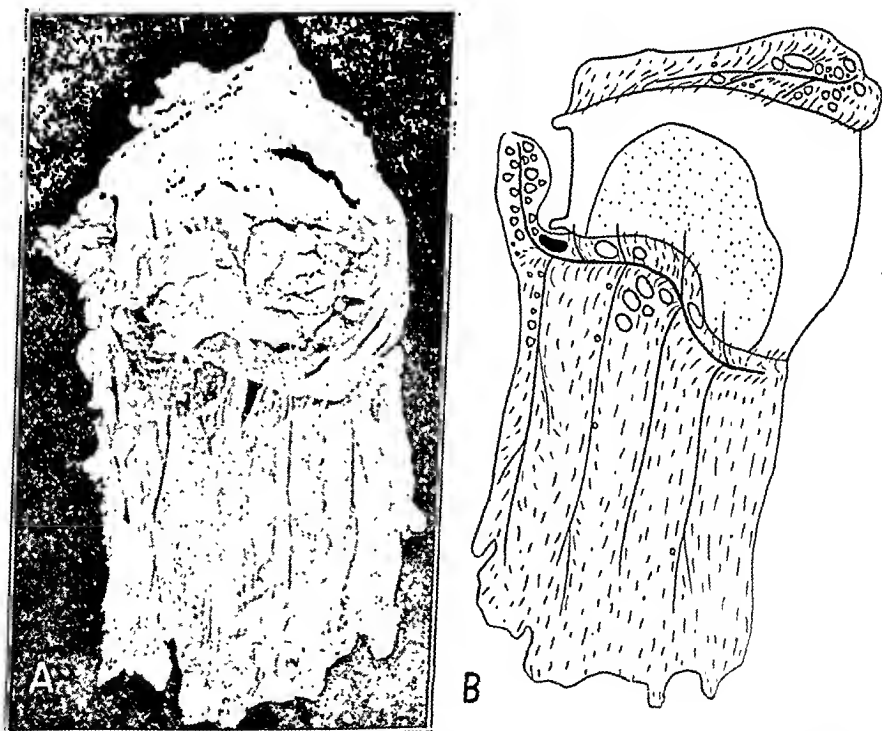


Fig. 7.—*A*, gross operative specimen of a carcinoma of the stomach, illustrating the wide margin of normal gastric wall removed about the lesion and the extensive resection of the adjacent gland-bearing ligaments, mesenteries and omentum. *B*, line drawing of this specimen, demonstrating that as a result of the extensive resection of the inferior gastric-subpyloric zone, the one and only positive lymph node was obtained.

LOCATION OF NEOPLASM WITHIN THE STOMACH IN RELATION TO
INCIDENCE AND LOCATION OF METASTASES

In most of the cases in this series the carcinoma was located either in the prepyloric region or in the pyloric antrum. In a number of instances the neoplasm in the pyloric antrum extended into the fundus of the stomach. In 2 cases it extended to the cardia. In 26 cases the carcinoma was completely annular; in 10 it was confined largely to the lesser curvature; in 7, to the anterior wall; in 5, to the greater curvature, and in 5, to the posterior wall. The incidence of metastases from carcinoma in these various locations, as well as the incidence of metastases in the various zones of lymphatic spread, is shown in table 1.

The conclusions to be drawn from table 1 are: (1) annular carcinoma is likely to spread to all zones; (2) a small neoplasm on the lesser curvature may metastasize to the nodes along the greater curvature:

TABLE 1.—*Local and Zonal Incidence of Metastasis*

Location	Cases	Cases in Which Metastases Occurred	Zone of Metastasis			
			Inferior Gastric-subpyloric	Pancreaticoduodenal	Superior Gastric	Supra-pyloric
Annular.....	26	22	22	5	14	9
Lesser curvature.....	10	5	5	0	5	1
Anterior wall.....	7	6	6	0	3	0
Greater curvature.....	5	3	3	1	0	1
Posterior wall.....	5	4	4	1	1	1

(3) a small neoplasm on the greater curvature may metastasize to the nodes along the lesser curvature; (4) a neoplasm located on either the anterior or the posterior wall may metastasize to the nodes along either curvature. Consequently, wide margins of the gland-bearing supportive tissues should be excised along both curvatures of the stomach, regardless of the location of the neoplasm.

SEX AND AGE IN RELATION TO LYMPHATIC METASTASIS

Metastasis to regional lymph nodes occurred in 35 of the men (77.7 per cent) and in 5 of the 8 women (62.5 per cent).

The average age of all the patients was 57.7 years. The average age of those with metastases was 57.2 years, in comparison with 59.7 years for those without. The 2 youngest patients were 40 and the oldest was 81 years of age. There were 13 below 50 years of age, 77 per cent of whom had metastases. There were 40 above 50 years, of whom 75 per cent had metastases. Age is not a factor in determining the incidence of metastases.

DURATION OF SYMPTOMS AND LYMPHATIC METASTASIS

The average duration of symptoms was thirteen and one one-hundredth months. For the group without metastases there was an average duration of thirteen and forty-five hundredths months; for the group with metastases it was twelve and eighty-seven hundredths. This difference is not striking, but it again emphasizes the fact that long duration of symptoms does not necessarily make the carcinoma inoperable or the prognosis less favorable. There were 5 patients with symptoms for over one year who were found to be free from regional lymphatic metastases. Several of these had been ill for two and three years. On the other hand, there were 6 patients whose symptoms had ranged from one to three months and who subsequently were found to have lymphatic metastases. Duration of symptoms alone should not influence the treatment advised.

SIZE OF NEOPLASMS AND LYMPHATIC METASTASIS

There was no relation between the size of the neoplasm and the presence of metastases. The largest neoplasm was 14 cm. in length and had not metastasized. The smallest neoplasm was 2 cm. in length and had metastasized. The average size was 7.37 cm. in length. Of the 26 neoplasms larger than average, 22 (84.7 per cent) had metastasized, compared to 18 (66.6 per cent) of the 27 lesions smaller than average. Five of the 6 largest neoplasms and 4 of the 6 smallest neoplasms were found to have metastasized. This emphasized the fact that radical operative resection should be done in patients having small tumors. Figure 8 illustrates a small carcinoma which at the time of operation was thought to be a large callus ulcer that had extensive metastases in the regional lymph nodes even though no palpable lymph nodes existed.

GROSS TYPE AND LYMPHATIC METASTASIS

The gastric carcinomas in our series were classified by their gross characteristics into three groups. The first group included 6 neoplasms which on gross examination were thought to be ulcers. Two of these were subsequently found to have resulted from carcinomatous proliferation at the edges of peptic ulcers, whereas a third accompanied two nearby peptic ulcers; the remainder were small ulcerating carcinomas. The second group included the sessile or plaquelike neoplasms which tended to infiltrate the wall of the stomach. The third group consisted of the large polypoid fungating neoplasms, many of which had ulcerating centers. A correlation of the gross types with lymphogenous metastases (table 2) shows (except for the ulcerating type) that the polypoid fungating neoplasms are less malignant than the sessile neoplasms. Five

of the 6 carcinomas infiltrating into muscle only were polypoid in character, and 2 had arisen on ulcers.

There were metastases in 4 (66.6 per cent) of the 6 cases of the ulcer type, too small a number from which to draw conclusions. However, 21 (95.4 per cent) of the 22 sessile carcinomas had metastasized, compared with 15 (60 per cent) of the 25 polypoid neoplasms. This emphasizes the highly malignant character of the sessile carcinomas.

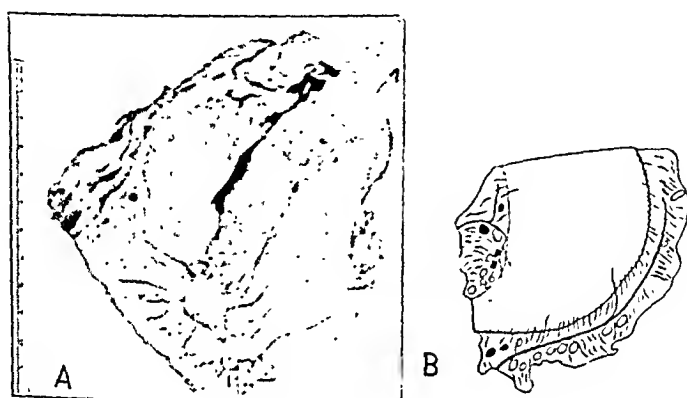


Fig. 8.—*A*, gross specimen of a carcinoma of the stomach following partial gastric resection, demonstrating a small ulcerated neoplasm of the lesser curvature near the pylorus. *B*, line drawing of the lymphatic metastases from the carcinoma in this specimen, demonstrating the large number of involved lymph nodes, even though this was not clinically suggested.

TABLE 2.—*Gross Types of Carcinoma Correlated with Lymphatic Metastasis*

Gross Type	Cases	Cases in Which Metastases Occurred	Per Cent
Ulcerous.....	6	4	66.6
Sessile.....	22	21	95.4
Polypoid.....	25	15	60.0

DEPTH OF INFILTRATION AND LYMPHATIC METASTASIS

Forty-seven of the 53 neoplasms had extensively infiltrated through the entire stomach wall and involved the serosa. Thirty-eight of these (80.8 per cent) had given rise to demonstrable metastases in regional lymph nodes. In 2 of the 5 specimens (40 per cent) in which the carcinomatous infiltration was confined to the muscular layer metastases were also found. The single carcinoma in which infiltration had extended into the submucosa only had not metastasized. Thus, the more extensive the depth of infiltration, the greater the possibility of metastasis to the regional lymph nodes.

DEGREE OF CELLULAR DIFFERENTIATION (GRADING) AND LYMPHATIC METASTASIS

The majority (31) of the carcinomas of the stomach were graded 3 as to cellular differentiation. There were 11 carcinomas graded 2 and 10 that were graded 4. Only 1 carcinoma was graded 1, and it

TABLE 3.—*Depth of Infiltration and Lymphatic Metastasis*

Depth of Infiltration	Cases	Cases in Which Metastases Occurred	Per Cent
Entirely through wall, with involvement of serosa.....	47	38	80.8
Infiltration into muscle layers.....	5	2	40.0
Infiltration into submucosa.....	1	0	0

TABLE 4.—*Cellular Differentiation and Lymphatic Metastasis*

Grade	Cases	Cases in Which Metastases Occurred	Per Cent
1.....	1	0	0
2.....	11	7	63.33
3.....	31	24	77.41
4.....	10	9	90.00

TABLE 5.—*Microscopic Type and Metastasis*

Type	Cases	Cases in Which Metastases Occurred	Per Cent
Medullary adenocarcinoma.....	6	6	100
Scirrhus adenocarcinoma.....	4	4	100
(a) Partly papilliferous.....	1	1	100
(b) Partly adenocarcinoma mucosum.....	5	5	100
(c) Partly adenocarcinoma.....	4	4	100
Adenocarcinoma mucosum.....	7	6	85.71
(a) Partly papilliferous adenocarcinoma...	1	1	100
Adenocarcinoma (simplex).....	16	9	56.25
(a) Partly adenocarcinoma mucosum.....	2	1	50
Papilliferous adenocarcinoma.....	7	3	42.85
Total.....	53	40	75.5

showed shallow infiltration at the base of a gastric polyp. Table 4 substantiates the dictum that the more anaplastic the neoplasm, the more likely the presence of lymphatic metastases.

MICROSCOPIC TYPE AND LYMPHATIC METASTASIS

In table 5 it will be noted that the neoplasms were distributed evenly among the various types except for adenocarcinoma (simplex). Medullary adenocarcinoma and scirrhus adenocarcinoma had the highest

incidence of metastases (100 per cent), and the tumors belonging to these types were all graded either 3 or 4, again showing that they tended to be more malignant. The type having the next highest incidence (85.7 per cent) of metastases was adenocarcinoma mucosum. The two types showing the least incidence of metastases were adenocarcinoma (simplex) (56.25 per cent) and papilliferous adenocarcinoma (42.85 per cent).

SUMMARY

An analysis of the incidence of metastases in regional lymph nodes in 53 cases of carcinoma of the stomach is presented.

As a result of the special method used in the investigation, evidence of metastases was found in 75.5 per cent of the cases in this study. This figure would more closely approximate 88 per cent if more nodes could have been obtained in cases in which operation was done for palliation alone.

Gastric carcinoma had involved the duodenum in 26.4 per cent of the cases.

The upper margin of the neoplasm in 24.5 per cent could not be determined by palpation alone at the time of operation.

The most important zones of lymphatic metastases are the inferior gastric-subpyloric and the superior gastric. Frequently, carcinomatous nodes are left in these zones even though all gross evidence of malignancy is removed.

There was no relation between duration of symptoms and lymphatic metastases.

There was no relation between the size of the neoplasm and the presence of lymphatic metastases. Small neoplasms were often associated with extensive nodal metastases.

Of the sessile neoplasms, 95.4 per cent had metastasized, in comparison with 60 per cent of the polypoid neoplasms.

The more anaplastic the carcinoma cells were, the higher the incidence of metastases was.

Medullary adenocarcinoma, scirrhus adenocarcinoma and adenocarcinoma mucosum were associated with the highest incidence of metastases. Adenocarcinoma (simplex) and papilliferous adenocarcinoma were associated with the lowest incidence of metastases.

In the majority of cases of carcinoma of the stomach in which the regional nodes were not palpable or, if palpable, were not thought to be suggestive of malignancy, the carcinoma was subsequently shown to have metastasized.

Whether palpable lymph nodes are present or not, the four zones of lymphatic metastases should be included within the resection to increase the likelihood of cure.

ACUTE CHOLECYSTITIS

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During the ten year period following Jan. 1, 1930 there were 2,273 patients operated on for nonmalignant extrahepatic disease of the biliary tract in the Massachusetts General Hospital, exclusive of the Phillips House private ward. Of this number, 415 patients, or 18.25 per cent of the whole, had acute cholecystitis. We selected the cases of these patients for study after a careful review of all the records. In every case the diagnosis was supported not only by the operator's opinion but by the pathologic report. All patients had symptoms of acute disease. In 85 per cent pain, tenderness, spasm, palpable mass, a temperature above 101 F. and a leukocyte count above 12,000 were present; with respect to the other 15 per cent, one or another of these findings was not recorded. The most common omission was the presence of a mass in the upper right quadrant of the abdomen. In every instance we were satisfied that the diagnosis was substantiated; if there was doubt, the case was excluded. Thus in 97 additional cases the disease was reported as acute, but the other requisites for the diagnosis were lacking. Many other cases in which the disease was considered acute by the operator were also excluded for the same reasons. We therefore believe that this report accurately represents our experience with acute inflammation of the gallbladder during the period under consideration.

In previous reports¹ we have shown that the mortality rate of simple cholecystectomy in this whole group of patients with chronic subacute and acute disease of the gallbladder was 2.45 per cent. If those whose disease was acute are eliminated, the mortality rate was 1.74 per cent. In those patients who underwent exploration of the common duct and who were found to have stones in the duct the mortality rate was 7.16 per cent; while in those who had exploration of the common duct with a negative result in addition to cholecystectomy the mortality was 2.04 per cent. In these 415 patients with acute cholecystitis the operative

From the Surgical Service of the Massachusetts General Hospital.

1. Allen, A. W., and Wallace, R. H.: *Technic of Operation on the Common Bile Duct*, Am. J. Surg. **28**:533-561 (June) 1935; *The Surgical Management of Stone in the Common Bile Duct*, Ann. Surg. **111**:838-847 (May) 1940.

mortality rate was 6.0% per cent. We are interested in determining if possible the factors influencing the morbidity and the mortality in these cases of acute cholecystitis. Much has been written concerning the matter but one feels that in many instances the classification of the disease process was not clear. This makes for confusion and has caused strong advocacy of immediate or early operation, on one hand, and delayed operation, on the other. Consideration of the time element has usually been restricted to the time after entry into the hospital with no attention given to the duration of the disease. Attempts have been made to emphasize the danger of gangrene and perforation. Some have stressed the desirability of cholecystectomy rather than cholecystostomy. It is our hope that the analysis of our cases will help to clarify some of these disputed points.

THE AGE FACTOR

Sanders² and others have called attention to the fact that the operative mortality rate of disease of the gallbladder is higher in older

TABLE 1.—*Age Incidence and Mortality in 415 Cases of Acute Cholecystitis*

Age Group	Cases	Deaths	
		Number	Per Cent
Under 40.....	80	1	1.2
40 to 49.....	116	5	4.3
50 to 59.....	127	11	8.6
60 to 69.....	60	7	11.7
Over 70.....	28	1	3.6

patients. This we believe has a dual meaning. The younger patient has fewer complicating disorders, but the older patient, on the other hand, has usually had infection of the biliary tract for a longer period of years and thus has more damage of the liver. This is an excellent argument against palliative management of disease of the gallbladder, especially when there are stones in the common duct. The risk of cholecystectomy in the early stages of the disease is far less than the risk of future trouble necessitating surgical intervention at a time when the hazard of operation is greatly increased. In 25 per cent of our patients, however, the first attack of acute pain was associated with acute cholecystitis. This we believe is an argument against delaying operation on the basis of a first attack.

Table 1 gives the age distribution in our cases together with the mortality rates. Table 2 gives the mortality statistics for those cases in which the patients were under and those in which the patients were

2. Sanders, R. L., in discussion on papers of Heyd, Parsons and Allen and Wallace, Tr. South. S. A. 52:182, 1939.

over 45 years of age. The 2 deaths in the younger group were due to massive pulmonary emboli; this was confirmed at autopsy in both instances.

GANGRENE AND PERFORATION

Since it has long been known that gangrene of the gallbladder often follows acute cholecystitis and that rupture of the gallbladder frequently takes place under these circumstances, we have analyzed our cases in

TABLE 2.—*Mortality Statistics in Cases in Which the Patients Were Under and in Cases in which the Patients Were Over 45*

	Under 45	Over 45
Cases.....	139	276
Deaths		
Number.....	2	23
Per cent.....	1.44	8.33

TABLE 3.—*Operative Mortality in Relation to Presence or Absence of Gangrene*

	Cases	Deaths	
		Number	Per Cent
Gangrene absent.....	292	11	3.75
Gangrene present.....	123	14	11.50
Total.....	415	25	6.06

TABLE 4.—*Operative Mortality in Relation to Presence or Absence of Perforation*

	Cases	Deaths	
		Number	Per Cent
Perforation absent.....	59	3	5.3
Perforation present.....	64	11	17.2
Total.....	123	14	11.5

regard to these factors. That the operative mortality is higher in the presence of gangrene with perforation is established, notwithstanding the infrequency of generalized peritonitis accompanying this complication. At the time of operation gangrene of the gallbladder was present in 29.4 per cent of all cases of acute cholecystitis, and in over half of these it had perforated the gallbladder. In 3 of these the process had perforated into the free peritoneal cavity, and there was general peritonitis at the time of operation.

The data shown in tables 3 and 4 indicate that operation for acute cholecystitis with or without gangrene is accompanied by a reasonably satisfactory mortality rate, unless perforation has taken place.

Inasmuch as gangrene with perforation occurs so frequently and is associated with such a high mortality rate, we attempted to find some indications by which these complications could be predicted. The age distribution of these cases as compared with the entire group is shown in chart 1 and eliminates the possibility of any help from this source.

The maximum temperature and the maximum leukocyte count, shown in tables 6 and 7, are likewise unreliable guides to the state of the disease process.

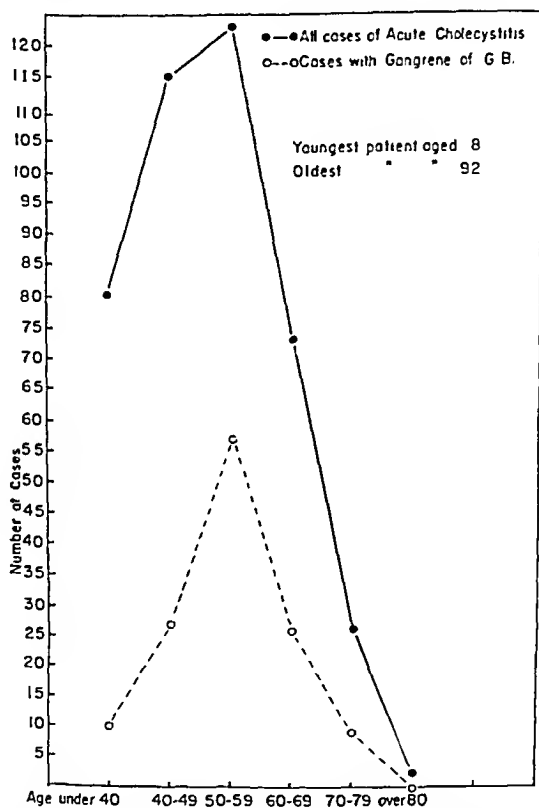


Chart 1.—Similarity of age distribution of acute cholecystitis to that of gangrene of the gallbladder. The peak appears in the fifth decade.

THE FACTOR OF DURATION OF SYMPTOMS

This factor was analyzed in relation to the mortality rate in all cases. Those in which there was gangrene and those in which there was gangrene with perforation were reviewed separately in this respect (chart 2).

Gangrene occurred prior to the fourth day of the disease in only 10 instances. There was no case in which perforation occurred prior to

this time, and there were only 3 instances in which it occurred between the fourth and the sixth day after onset; all 3 of the patients recovered.

The average duration of symptoms before operation for all 415 cases of acute cholecystitis was eight and nine-hundredths days (chart 3). In

TABLE 5.—Operative Mortality in Relation to Abscess, Local Peritonitis and General Peritonitis Following Perforation

	Cases	Deaths	
		Number	Per Cent
Perforation with abscess.....	52	8	15
Perforation with local peritonitis.....	9	0	0
Perforation with general peritonitis.....	3	3	100
Total.....	64	71	17.2

TABLE 6.—Maximum Preoperative Temperature

	Temperature Over 102 F.		Temperature Over 103 F.	
	Number	Per Cent	Number	Per Cent
All cases (415).....	202	48.6	88	21.2
Cases with gangrene (123).....	53	47.1	24	19.5

TABLE 7.—Maximum Preoperative Leukocyte Count

	Leukocyte Count Over 20,000	
	Number	Per Cent
All cases (415).....	106	25.5
Cases with gangrene (123).....	41	33.3

TABLE 8.—Operative Mortality in Relation to the Duration of Symptoms Before Operation

	Cases	Deaths	
		Number	Per Cent
4 days or less.....	108	3	2.77
5 to 8 days.....	133	9	6.78
9 days or more.....	174	13	7.47

26 per cent of the cases operation had been performed by the fourth day of the disease; in 42 per cent there was a delay of nine days or more after symptoms appeared before operation was undertaken.

Among the 108 cases in which operation was performed by the fourth day after the onset of the disease there were 3 deaths, 2 from post-operative pneumonia and 1 from pulmonary embolism. The mortality rate increased materially after this time. During the period covered by

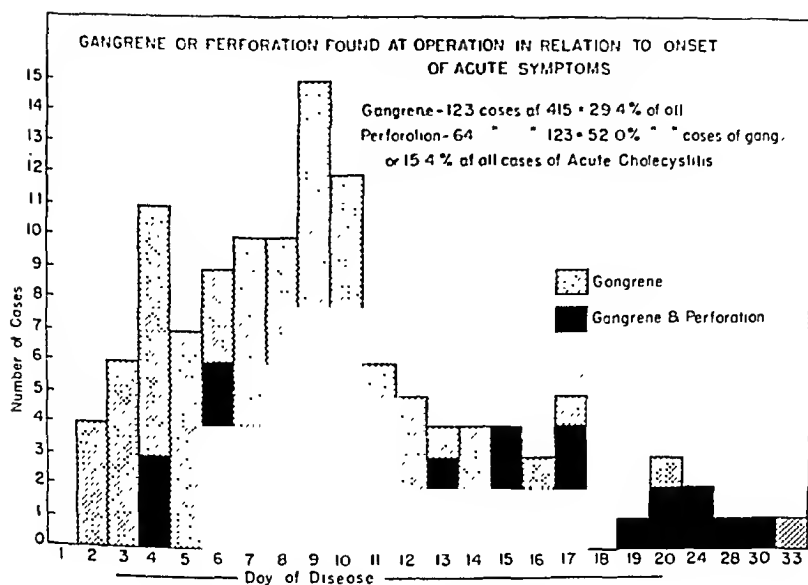


Chart 2.—Duration of disease at operation when gangrene or gangrene together with perforation was found. In the cases of perforation before the sixth day after the onset of symptoms the perforations were all early, and all 3 patients recovered.

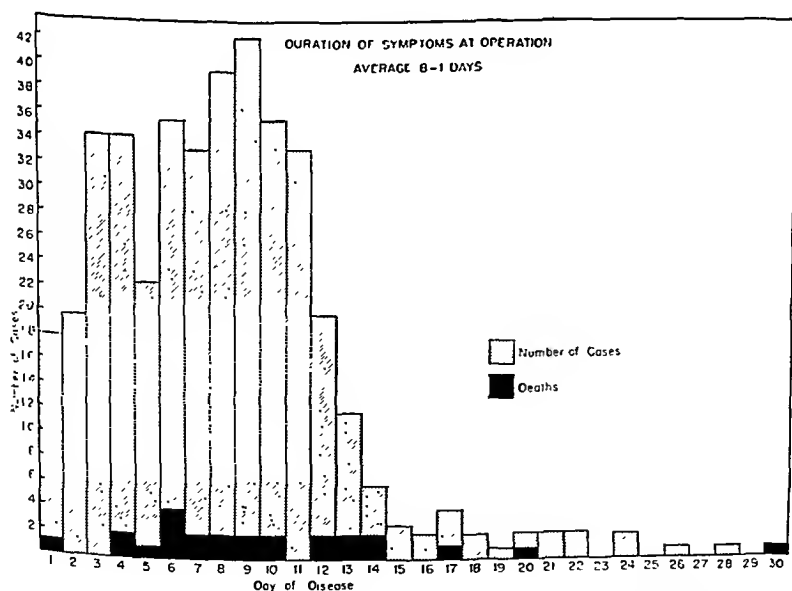


Chart 3.—Duration of disease at operation and deaths in all cases of acute cholecystitis. The 3 deaths of patients operated on within four days after onset of symptoms were not directly related to the primary disease.

this study the majority of the hospital staff favored delayed operation in acute cholecystitis. We must admit that we were strong advocates of careful observation of the patients and of operating only when there was failure of steady improvement, hoping that a subacute phase might be reached, which we felt offered a safer time for operation. We thought that by so doing we could avoid cholecystostomy and remove the gallbladder more often. Also we believed that perforation, if it did occur, would produce a localized process that would not greatly interfere with an adequate procedure and recovery. Miller³ felt that early operation was desirable in such cases, although he had not been able at the time of his publication to gather sufficient data to support his view strongly.

Forty-four patients in this group were subjected to emergency operation within four hours of admission to the hospital. Seventeen of these were operated on after a mistaken diagnosis, 11 for acute appendicitis and 6 for perforated peptic ulcer. There were 4 deaths in this group, 2 from general peritonitis present at the time of operation and 2 from pulmonary complications after lengthy surgical procedures. Thus it is not evident from our statistics that emergency operation for acute cholecystitis is particularly hazardous, since 2 of the patients would certainly not have benefited by delay. It is evident to us all, however, that delay is indicated until chemical balance and hydration have been cared for. Since an adequate team is important, this operation is a poor one for the middle of the night.

Certainly we cannot place much of the blame for delay on our patients, or their physicians, since 71.3 per cent of the patients sought relief in the hospital by the fourth day after the onset of symptoms (chart 4). The average duration of symptoms on admission for all 415 patients was three and a half days; the average period of hospital delay from admission to operation was four and three-fifths days. There were only 3 deaths in the series which could be considered due to delay on the part of the patient.

Our policy of waiting has allowed us to study the results of this type of management. The duration of symptoms on admission and the duration of symptoms at operation of all cases of perforation of the gallbladder are shown in chart 5. Thirty-four of the patients entered the hospital before the fifth day of symptoms, and 30 of these doubtless suffered perforation of the gallbladder while under observation in the hospital. Since we can find no reliable criteria to indicate the presence of gangrene and perforation, we must change our policy from one of watchful waiting to one of operating as soon as the optimum conditions as regards both the patient and the operating facilities are established.

3. Miller, R. H.: Acute Cholecystitis, *Ann. Surg.* 92:644-648 (Oct.) 1930.

CHOLECYSTECTOMY AND CHOLECYSTOSTOMY

We realize that there are many factors not taken account of in a study of records and that the evidence pointing to cholecystectomy as

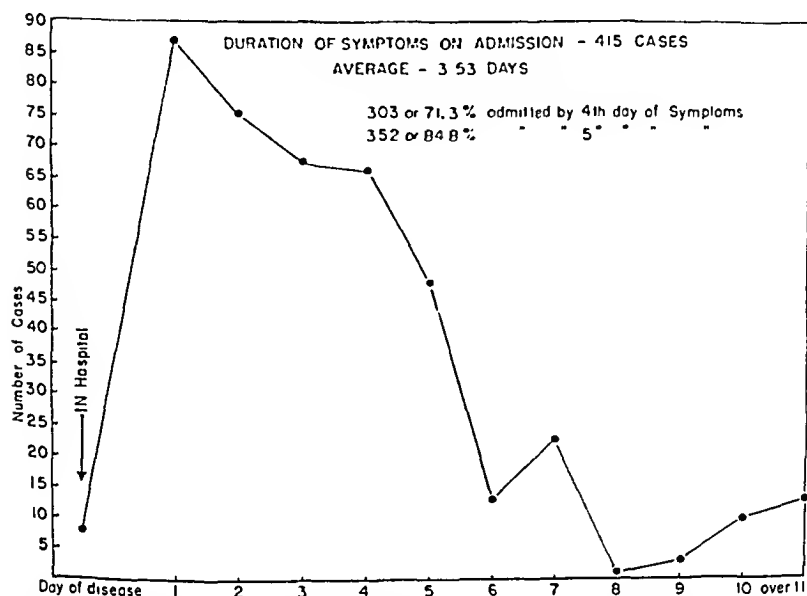


Chart 4.—Duration of symptoms on admission. Most patients sought early relief at the hospital.

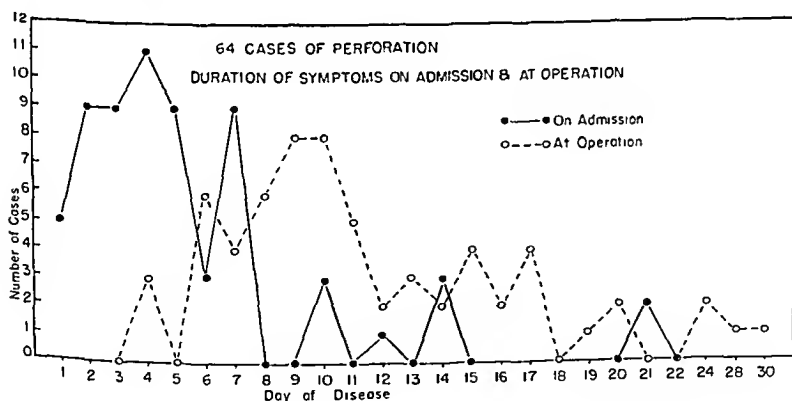


Chart 5.—Duration of symptoms on admission and at operation of all patients with perforated gallbladders. The majority were admitted early and were operated on late. Forty-three patients were admitted by the fifth day after the onset of symptoms.

a safer procedure than cholecystostomy is probably subject to much criticism.

Subsequent cholecystectomy was performed on 27 of 127 patients who survived cholecystostomy; there were 3 deaths, a mortality rate of 11.1 per cent for secondary cholecystectomy. In addition, 12 patients had typical biliary colic, and 6 had persistent sinus and refused operation. It is probable that others had secondary operations elsewhere. Only 28.3 per cent of the patients were discharged as well before seventeen days after cholecystostomy, in comparison with 59.3 per cent discharged as well before seventeen days after cholecystectomy. Of survivors after cholecystectomy, 14 per cent remained in the hospital longer than twenty days, while 39.3 per cent of survivors after cholecystostomy remained in the hospital longer than twenty days. It is reasonable that the removal of an infected or gangrenous structure greatly enhances the recovery of the host. Table 9 shows various figures for comparison.

TABLE 9.—*Comparative Data on Cholecystectomy and Cholecystostomy*

	Cholecystectomy	Cholecystostomy
Average age of patients.....	50.1	55.2
Average duration of symptoms before admission (days)...	3.5	3.5
Average delay of operation after admission (days).....	4.8	4.1
Patients with preoperative temperature of 103 F.....	43	45
Patients with preoperative leukocyte count over 20,000....	55	51
Patients with gangrene of the gallbladder.....	68	55
Patients with gangrene with perforation of the gallbladder	24	40
Average stay of survivors in hospital (days).....	18.0	26.1
Mortality rate (per cent).....	3.3	11.1
Total number of cases.....	272	143

As more than one third of all patients were subjected to cholecystostomy, we were interested in whether or not they were chiefly those who delayed hospital admission or were old or debilitated or extremely ill. The records showed that 58 per cent of them entered the hospital within three days after the onset of symptoms and 73.4 per cent within four days after the onset of symptoms. This is a greater percentage of early admissions than was found for those patients who had cholecystectomy. Only 50 of 143 patients who had cholecystostomy were over 60 years of age, and fewer patients with preoperative temperatures over 103 F. and leukocyte counts over 20,000 had cholecystostomy than cholecystectomy. Undoubtedly cholecystostomy was a life-saving measure in numerous cases, but there is no evidence that the majority of the patients were poorer risks than those who had their gallbladders removed. There was a preoperative hospital delay of three days or longer for 53 per cent of patients who had cholecystostomy, and we believe that many of this group could have safely had their gallbladders removed if they had been operated on at an earlier stage of the disease, when the state of inflammation offers much less technical difficulty.

We believe that drainage of the gallbladder with the area under local anesthesia is indicated for the feeble or gravely ill patient and that operation early in the disease will make this an infrequent procedure.

There was no record of stone in the gallbladder in 5.3 per cent of all cases, but no definite mention of absence or failure to find stones was made in many of these cases.

Diabetes requiring insulin was found in 6 per cent of all cases, and the mortality rate in this group was 8 per cent.

Jaundice was present at operation in 45 patients; 16 of these had one or more stones removed from the common duct. Jaundice cleared

TABLE 10.—*Chief Cause of Death*

Cause	Cases	Cause	Cases
Peritonitis.....	10	Cerebral hemorrhage.....	1
".....	7	Hepatic infarct.....	1
".....	4	Total.....	25
".....	2		

TABLE 11.—*Complications Necessitating Hospitalization for More than Twenty Days*

Complication	Cases
Wound infection	43
Prolonged fever without explanation.....	11
Thrombophlebitis	11
Wound dehiscence	4
Pneumonia	2
Prolonged drainage of bile.....	5
Cardiac lesions	2
Subdiaphragmatic abscess	2
Residual abdominal abscess.....	1
Miscellaneous	5
No explanation (mostly private cases).....	15
Total.....	102

spontaneously in 29 patients without removal of a stone from the common duct. In 6 of these, no abnormalities were found on exploration of the common duct. Exploration of the common duct was performed on 28 patients who had cholecystectomy; there were 2 deaths, a mortality rate of 7.1 per cent. Exclusive of cases in which operation was performed on the common duct there were 244 in which cholecystectomy was done; there were 7 deaths, a mortality rate of 2.9 per cent.

The average postoperative hospital period for survivors was nineteen days. Of all patients, 46.5 per cent were discharged as well before seventeen days, and 22.5 per cent of the survivors remained in the hospital longer than twenty days.

The chief causes of death are shown in table 10; peritonitis was the most common cause.

Complications of survivors which necessitated hospitalization for more than twenty days are shown in table 11.

SUMMARY AND CONCLUSIONS

Gangrene and perforation are the factors which most strikingly increase the operative mortality in acute as compared with nonacute cholecystitis.

With conservative treatment, even under careful observation in the hospital, gangrene with perforation cannot be anticipated and frequently progresses to a dangerous stage.

Gangrene with perforation is unusual before the sixth day after the onset of symptoms.

Operation within four days of the onset of symptoms is relatively safe if there has been proper preoperative preparation.

Cholecystectomy is the procedure of choice.

Early intervention would practically eliminate the hazard of gangrene with perforation in the patients coming to the hospital.

ALIMENTARY AZOTEMIA AND THE BLEEDING PEPTIC ULCER SYNDROME

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AND

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DETROIT

Since 1933, when Sanguinetti¹ first called attention to increased amounts of urea nitrogen in the blood of patients with bleeding peptic ulcer, this observation has been confirmed by many writers. These include Sanguinetti himself² (1933), Christiansen³ (1935, 1936, 1937), Ingegno⁴ (1935), Meyler⁵ (1935, 1936), Sučić⁶ (1935), Alsted⁷ (1936), Borst⁸ (1936, 1938), Clausen⁹ (1936) and Polack¹⁰ (1936).

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1. Sanguinetti, L. V.: *Curvas azohemicas en las hemorragias retenidas del tubo digestivo*, Arch. argent. de enferm. d. ap. digest. y de la nutrición 9:68-75 (Oct.-Nov.) 1933; cited by Schiff and others.³⁵

2. Sanguinetti, L. V.: *Azoemias en el curso de las hemorragias retenidas a nivel del tubo digestivo (estudio clínico y experimental)*, Arch. argent. de enferm. d. ap. digest. y de la nutrición 9:264-287 (Feb.-March) 1934.

3. Christiansen, T.: (a) *Uraemia as Cause of Death in Massive Haemorrhage from Peptic Ulcer*, Acta med. Scandinav. 85:333-345, 1935; (b) *Hyperazotaemia in Intraintestinal Haemorrhage*, ibid., 1936, supp. 78, pp. 894-899; (c) *Biochemical Changes in the Organism Produced by Massive Intra-Intestinal Hemorrhage*, Rev. Gastroenterol. 4:166-180 (Sept.) 1937.

4. Ingegno, A. P.: *The Elevated Blood Urea of Acute Gastro-Intestinal Hemorrhage and Its Significance*, Am. J. M. Sc. 190:770-774 (Dec.) 1935.

5. Meyler, L.: (a) *Post-Haemorrhagic Uraemia*, Acta med. Scandinav. 87:313-325, 1935; (b) *Uraemia Due to Dehydration*, ibid. 90:475-488, 1936.

6. Sučić, D.: *Akute Azotämie bei grossen gastrointestinalen Blutungen*, Klin. Wchnschr. 14:1316-1318 (Sept. 14) 1935.

7. Alsted, G.: (a) *Studies on Azotaemia After Haematemesis and Melaena*, Acta med. Scandinav., 1936, supp. 78, pp. 900-907; (b) *Further Studies on Azotemia Following Hemorrhage in the Digestive Tract*, Am. J. M. Sc. 192:199-208 (Aug.) 1936.

8. Borst, J. G. G.: (a) *Ueber Erhöhung des Kochsalz- und Harnstoffgehaltes und Erniedrigung des Albumingehaltes des Blutes bei Patienten mit starken Magenblutungen*, Ztschr. f. klin. Med. 130:75-96, 1936; (b) *The Cause*

(Footnotes continued on next page)

There have been at least sixteen other reports during the past five years; these will be quoted later. Although this syndrome has apparently been recognized over a period of only eight years, it is of considerable importance. The time has come to take stock and to appraise the significance, cause and mechanism of this syndrome.

SIGNIFICANCE OF AZOTEMIA

In some early studies the opinion was expressed that renal or hepatic damage was the cause of the elevation in urea nitrogen content of the blood accompanying bleeding peptic ulcer. If renal or hepatic damage is the cause, operation is contraindicated. If, on the other hand, azotemia is due to the presence of blood in the intestinal tract, its continuance indicates persistent bleeding and in a doubtful case perhaps argues for surgical intervention. The whole question of operative treatment of bleeding peptic ulcer is so debatable at present that any added information that offers aid in making this difficult decision is of value.

Prognostic Value.—Independent of its importance as a therapeutic guide, azotemia seems to be of definite prognostic import in cases in which operation has not been performed. Witts¹¹ (1937) and Ingegno⁴ (1935) both expressed their belief that the presence of azotemia is of prognostic significance. Ingegno stated: "Persistent elevation may point to persistent hemorrhage." Christiansen^{3c} (1937) also stated his opinion that azotemia is of prognostic value; he said: "A slight or transitory rise in the blood urea concentration is suggestive of a good prognosis, whereas high blood urea values—eventually increasing progressively—are to be looked upon as a poor prognostic sign." Yuile and Hawkins¹² (1941) did not credit azotemia with much value in prognosis.

Schiff and Stevens¹³ (1939), on the other hand, stated that "its value in prognosis should, in turn, make it an aid to therapeutic management of Hyperchloremia and Hyperazotemia in Patients with Recurrent Massive Hemorrhage from Peptic Ulcer, Acta med. Scandinav. 97:68-88, 1938.

9. Clausen, J.: Hyperazotemia in Cases of Acute Ventricle Hemorrhage, Acta med. Scandinav., 1936, supp. 78, pp. 908-914.
10. Polack, E.: Azotemia After Hematemesis, Acta med. Scandinav., 1936, supp. 78, pp. 914-915.
11. Witts, L. J.: Haematemesis and Melaena, Brit. M. J. 1:847-852 (April 24) 1937.
12. Yuile, C. L., and Hawkins, W. B.: Azotemia Due to Ingestion of Blood Proteins: Blood Urea Increase Related to Ingestion of Whole Blood, Red Cells, Plasma and Other Proteins, Am. J. M. Sc. 201:162-167 (Feb.) 1941.
13. Schiff, L., and Stevens, R. J.: Elevation of Urea Nitrogen Content of the Blood Following Hematemesis or Melena, Arch. Int. Med. 64:1239-1251 (Dec.) 1939.

ment" and that "the urea nitrogen content of the blood should be repeatedly estimated in all cases of hematemesis or melena because of its prognostic significance."

Schiff¹⁴ (1940) especially emphasized the prognostic significance of an increase of the urea nitrogen content of the blood after hematemesis and melena. In a series of 135 cases, the urea nitrogen was found to exceed 30 mg. per hundred cubic centimeters in 78 of the cases and to be 50 mg. or more in 26 of these 78 cases. Thirteen, or 16.9 per cent, of the patients with a urea nitrogen content of the blood of 30 mg. or more died; 9, or 34.6 per cent, of those with an elevation of 50 mg. or more died, and 7, or 63.6 per cent, of those with an elevation of 70 mg. or more died. Among the 57 patients with a blood urea nitrogen con-

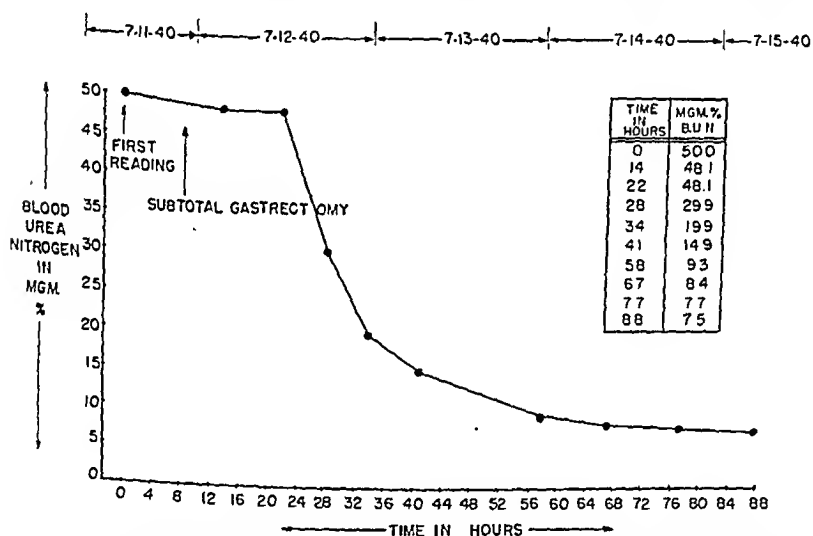


Chart 1.—Decline in the urea nitrogen level of the blood following gastric resection in a patient with bleeding peptic ulcer. B. U. N., urea nitrogen content of the blood.

tent of less than 30 mg. there were no deaths except 2 due to ruptured aortic aneurysm.

Our own data on this aspect of the subject are not extensive enough to lead to any conclusions. However, we wish to cite the case of a patient 49 years of age with bleeding of several days' duration. Because of the lack of improvement after being subjected to a conservative regimen and because of the high urea nitrogen content of the blood (chart 1) gastric resection was performed. The patient recovered. At operation a spurting branch of the pancreaticoduodenal artery was observed in the

14. Schiff, L.: Azotemia Following Hemorrhage, personal communication to the author, May 1940.

base of the ulcer. In another case, in which the patient died from post-operative bleeding after gastric resection, the urea nitrogen content of the blood ranged from 60 to 95 mg. per hundred cubic centimeters during the last five days of life. Holman¹⁵ (1940) reported that in 2 of his 90 cases of bleeding peptic ulcer the urea nitrogen contents of the blood were high and rose until the time of death.

CAUSES OF AZOTEMIA

Numerous causes of azotemia accompanying hematemesis and melena have been considered by various authors (table 1). The most obvious classification of azotemia (and also of uremia) is according to renal and

TABLE 1.—Factors Proposed by Various Authors as the Cause of the Rise in the Urea Nitrogen of the Blood Associated with Intraintestinal Hemorrhage

Author	Date	Proposed Causes *
Sanguinetti.....	1934	Blood absorption, increased protein catabolism and chloro-penia
Ingegno.....	1935	Blood absorption, hemorrhage, shock, dehydration and starvation
Meyler.....	1935	Dehydration, increased protein catabolism and blood absorption
Sučić.....	1935	Shock (producing decrease of renal function) and increased protein catabolism
Alsted.....	1936	Shock (producing decrease of renal function), dehydration, and blood absorption
Clausen.....	1936	Blood absorption and increased protein catabolism
Borst.....	1938	Blood absorption and decreased renal function due to shock
Witts.....	1937	Shock
Crohn.....	1939	Blood absorption
Schiff and co-workers..	1939	Blood absorption and increased protein catabolism
Kaump and Parsons...	1940	Blood absorption
Chunn and Harkins...	1940	Blood absorption
Yulle and Hawkins....	1941	Blood absorption

* The factor assigned the chief role is listed first.

extrarenal types. First consideration will therefore be given as to whether or not the azotemia under consideration is renal azotemia.

Renal Azotemia.—Sanguinetti² (1934), Christiansen^{3a} (1935) and Ingegno (1935) found no evidence of renal impairment in their cases of hematemesis. Alsted^{7b} (1936) observed a fall in the urea clearance to 15 per cent of normal in the presence of organically normal kidneys in a fatal case of hematemesis with a blood urea concentration of 216 mg. per hundred cubic centimeters.¹⁶ He attributed the decrease of renal function to low blood pressure and diminished renal blood flow. In 4 other cases with less marked azotemia there was no reduction in renal

15. Holman, C. W.: Severe Hemorrhage in Gastric and in Duodenal Ulcer: A Study of Ninety Cases, Arch. Surg. 40:150-160 (Jan.) 1940.
16. Alsted was one of many who expressed his results in urea rather than urea nitrogen as we have done. Since the values for the former are two and fourteen hundredths times those for the latter, the difference is appreciable.

clearance. Clausen (1936), Borst (1936 and 1938), Black¹⁷ (1939) and Witts¹¹ (1937) all found decreased renal function in some of their cases.

The most extensive observations on this aspect of the question were those of Stevens, Schiff, Lublin and Garber¹⁸ (1940). They concluded on the basis of their studies: "The reduction in the urea clearance may be due to the decreased renal blood flow but is insufficient to account for the increased blood urea content and persists in spite of the return of the blood urea nitrogen to normal. The elevation of the blood urea nitrogen content which follows hematemesis in the absence of shock is not due to impairment of kidney function." Johnson¹⁹ (1940) observed no increase in blood urea nitrogen content in the absence of renal damage in patients who were fed blood by a stomach tube. However, Johnson did not state either the amounts of blood administered or the intervals afterward at which the determinations were made. Harris²⁰ (1940) stated that the rise of blood urea after hemorrhage is most likely due to the fall of blood pressure and probably has nothing to do with the hemorrhage as such. Lowered blood pressure in interfering with renal activity would cause accumulation of urea in the blood. Kaump and Parsons²¹ (1940) stated: "From a study of the urea ratio values, we can probably eliminate renal failure as a factor."

It seems that any conclusions drawn cannot be applied to all clinical patients. Many patients have renal damage in addition to bleeding ulcer. In fact there are two reasons why patients with bleeding ulcer are especially prone to renal insufficiency: one of these is the possibility of renal damage from prolonged alkaline therapy; the second is that patients with arteriosclerosis—and hence possibly with renal insufficiency—are especially apt to continue bleeding once the latter begins. It is therefore impossible to state in each case that none of the azotemia is due to renal insufficiency.

An Experiment: Four experiments were performed on 2 dogs. Both these dogs had roentgen nephritis produced by the method of Hart-

17. Black, D. A. K.: Urea Clearance in Haematemesis, *Lancet* 1:323-325 (Feb. 11) 1939.

18. Stevens, R. J.; Schiff, L.; Lublin, A., and Garber, E. S.: Renal Function and the Azotemia Following Hematemesis, *J. Clin. Investigation* 19:233-237 (Jan.) 1940.

19. Johnson, J. B.: The Pathogenesis of Azotemia in Hemorrhage from the Upper Gastro-Intestinal Tract, *J. Clin. Investigation* 19:776 (Sept.) 1940.

20. Harris, I.: Blood-Urea and Plasma Chloride in Experimental Haemorrhage, *Lancet* 2:795-796 (Dec. 21) 1940.

21. Kaump, D. H., and Parsons, J. C.: Extrarenal Azotemia in Gastro-Intestinal Hemorrhage: I. General and Clinical Consideration, *Am. J. Digest. Dis.* 7:189-190 (May) 1940.

man. In all experiments there was a rise in the urea nitrogen of the blood after the giving of blood by a stomach tube. This rise differed from that resulting in normal dogs only in that its duration was a matter of several days rather than of less than twenty-four hours. The degree of rise was no greater than in normal dogs.

Extrarenal Azotemia.—The whole question of extrarenal azotemia was reviewed by Wohl, Brust and Freed²² (1938). They listed fifteen possible causes of extrarenal azotemia. It is becoming more and more recognized that azotemia often results from causes outside the kidney. Lemmer and Malec²³ (1939) reported an instance of extrarenal azotemia after drainage of the common duct. Adrenal insufficiency may produce azotemia. Swingle, Pffiffer, Vars and Parkins²⁴ (1934) stated that this syndrome "is probably extrarenal in origin." The liver also is closely bound up in the production of azotemia. Polack¹⁰ (1936) expressed the opinion that toxic action on the liver played a role in causing azotemia after intrainestinal bleeding. As a prophylactic against this effect, he advised the injection of a solution of dextrose. Other factors that may be important in causing azotemia associated with bleeding peptic ulcer are as follows:

(a) Starvation: Schiff and Stevens¹³ (1939) pointed out that since their patients were adequately fed, starvation could not be a factor. This likewise applies to most of the cases reported from Denmark by Alsted,⁷ Christiansen³ and others; the patients were treated by the Meulengracht diet.

(b) Dehydration: The role of dehydration was especially emphasized by Meyler^{5b} (1936). He pointed out that in cases of gastric hemorrhage the output of urea is larger than may be accounted for by the absorption of lost blood; although part of it may be due to absorption, dehydration accounts for the rest. In a series of 53 instances of hematemesis or melena, Schiff and Stevens¹³ (1939) observed that "as the level of urea nitrogen in the blood was frequently observed to rise during hospitalization in the presence of adequate administration of fluid it is believed that dehydration can be excluded as an essential factor in its increase." In our own experiments dogs given three subcutaneous injections of physiologic solution of sodium chloride daily and at the same time receiving blood by a stomach tube did not have such extensive azo-

22. Wohl, M. G.; Brust, R. W., and Freed, H.: Nonrenal Azotemia, *J. Lab. & Clin. Med.* **23**:450-458 (Feb.) 1938.

23. Lemmer, K. E., and Malec, J. P.: Drainage of the Common Bile Duct with Resultant Extrarenal Azotemia, *Arch. Surg.* **39**:125-130 (July) 1939.

24. Swingle, W. W.; Pffiffer, J. J.; Vars, H. M., and Parkins, W. M.: The Relation Between Blood Pressure, Blood Urea Nitrogen and Fluid Balance of the Adrenalectomized Dog, *Am. J. Physiol.* **108**:428-437 (May) 1934.

temia as dogs receiving blood alone, despite the fact that the latter were allowed to drink water freely. In all cases, however, definite azotemia resulted.

(c) Hemorrhage: Meyler²⁵ (1935) and Vallery-Radot²⁶ produced azotemia in animals by repeated bleeding. Corbet²⁶ (1940) reported an unusual case of accidental hemorrhage in which the patient died of uremia. She was a woman aged 37 who was thirty weeks gravid. The bleeding was not severe, and since it was from the uterus to the outside, the possibility of absorption was slight. The experiments of Kaump and Parsons²⁷ (1940) are especially instructive. They showed that while hemorrhage will produce azotemia the elevation in blood urea nitrogen after the intragastric administration of blood to dogs is independent of hemorrhage.

(d) Anemia: Meyler²⁵ (1935) stated that "the uraemia is not directly caused by anemia." Taylor and Lewis²⁸ (1915) demonstrated that anemia alone will not cause azotemia, and Schiff and Stevens¹² (1939) found no correlation between anemia and azotemia accompanying hematemesis or melena. Our own experimental results bear out this lack of correlation.

(e) Shock: Goldring²⁹ (1937) did not believe that absorption of lost blood can account for the increase of urea in the blood accompanying intestinal hemorrhage. Both he and Crohn³⁰ (1939) attributed the rise to shock. Schiff and Stevens¹² (1939) in their series of 53 cases of hematemesis or melena found that "elevation of the urea nitrogen content of the blood occurred in the absence of shock," and that "shock is not an essential factor in the elevation of the blood urea nitrogen which follows hematemesis."

(f) Hypochloremia: That hypochloremia and alkalosis accompanying protracted vomiting may be associated with azotemia is well known. A patient with a bleeding ulcer, however, seldom vomits more than once or twice. The relation between hypochloremia and azotemia has recently been studied by Kirsner and Palmer³¹ (1941). They showed that administration of chlorides by mouth relieves azotemia associated with

25. Vallery-Radot, P., cited by Christiansen.^{2c}

26. Corbet, R. M.: Uraemia After Accidental Haemorrhage, *Brit. M. J.* 2: 757-758 (Nov. 30) 1940.

27. Kaump, D. H., and Parsons, J. C.: Extrarenal Azotemia in Gastro-Intestinal Hemorrhage: II. Experimental Observations, *Am. J. Digest. Dis.* 7: 191-194 (May) 1940.

28. Taylor, A. E., and Lewis, H. B.: A Study of the Protein Metabolism Under Conditions of Repeated Hemorrhage, *J. Biol. Chem.* 22:71-75, 1915.

29. Goldring, W., in discussion on Christiansen.^{2c}

30. Crohn, B. B., in discussion on Schiff and others.³⁵

31. Kirsner, J. B., and Palmer, W. L.: The Role of Chlorides in Alkalosis Following the Administration of Calcium Carbonate, *J. A. M. A.* 116:384-390 (Feb. 1) 1941.

alkalosis. They also pointed out, however, that hypochloremia can exist without accompanying azotemia; this had been noted previously by Kerpel-Fronius³² (1936) and by Kirsner himself³³ (1941). Likewise, the investigations by Courriades³⁴ (1934) of experimental hypochloremia in dogs showed that hypochloremia is not necessarily accompanied by azotemia. It is of interest that Borst³⁵ (1938) found hyperchloremia in association with azotemia in his cases. Kaump and Parsons²¹ (1940) concluded from their clinical observations that "the blood chloride concentration per se has little to do with the elevation in blood urea" and from their experiments with animals they²⁷ concluded that "hypochloremia per se has nothing to do with the azotemia of gastro-intestinal hemorrhage."

(g) Increased Protein Catabolism: Increased protein catabolism was presented as an accessory factor by Meyler^{5a} (1935), Sučić⁶ (1935), Borst³⁵ (1938) and Kaump and Parsons²¹ (1940).

(h) Loss of Body Electrolytes: Wohl, Brust and Freed²² (1938) considered the loss of body electrolytes an important factor.

(i) Absorption of Lost Blood: It is our belief that absorption of lost blood is one of the most important items in the production of azotemia accompanying intrainestinal hemorrhage. This does not mean that certain of the already listed mechanisms may not play an important role, but it is true that blood in the intestinal tract alone will produce marked azotemia.

MECHANISM OF THE PRODUCTION OF AZOTEMIA BY BLOOD IN THE INTESTINAL TRACT

The importance of blood in the intestinal tract in the causation of azotemia was recognized by Sanguinetti¹ (1933), the first worker on the subject, as well as by others (table 1). Sanguinetti² (1934) in his classic paper on the subject stated: "the increase of the blood urea was due in our cases to absorption from the intestinal tract of a considerable quantity of proteins." He also stated that an increase of protein catabolism and chloropenia played subsidiary roles. Schiff¹⁴ (1940) stated: "It is felt that the digestion and absorption of the blood in the upper part of the digestive tract is the chief cause of elevation of the blood urea nitrogen."

Experimental Observations in Man.—Sanguinetti² (1934), Meyler^{5a} (1936), and Schiff and co-workers³⁵ (1939) fed blood to patients, and

32. Kerpel-Fronius, E.: Salzangelzustände und chloroprive Azotämie, *Ergebn. d. inn. Med. u. Kinderh.* 51:623, 1936.

33. Kirsner, J. B.: The Production of Hypochloremia Without Azotemia, to be published.

34. Courriades, J., cited by Alsted.^{7b}

35. Schiff, L.; Stevens, R. J.; Goodman, S.; Garber, E., and Lublin, A.: Observations on the Oral Administration of Citrated Blood in Man: I. The Effects on the Blood Urea Nitrogen, *Am. J. Digest. Dis.* 6:597-602 (Nov.) 1939.

azotemia resulted. Sučić⁶ (1935) and Clausen⁹ (1936) made a similar experiment but obtained no elevation in the urea nitrogen level of the blood. At least in Sučić's case, this may have been because of too infrequent determinations. Christiansen³⁶ (1937) gave 400 Gm. of veal to normal men in one dose. Only a slight postprandial rise of the urea in the blood occurred. The experiments of Schiff and associates³⁵ using both blood and meat so outnumbered those of all other experimenters combined and in addition were followed by so many more analyses of the blood, that there can be little doubt that feeding large amounts of blood or meat to normal persons will produce postprandial azotemia.

Experimental Observations in Animals.—Except for a few inconclusive experiments with rabbits by Sanguinetti² (1934), the first extensive series of experiments on the effect of feeding blood to animals was reported by Kaump and Parsons²⁷ (1940). Other animal experiments reported by Chunn and Harkins³⁶ (1940, 1941) and by Yuile and Hawkins¹² (1941) will be listed along with some original experiments.

(a) Effect of Whole Blood: A uniform rise in the urea nitrogen of the blood followed intragastric administration of whole blood to dogs.

(b) Effect of Intraperitoneal Injection of Blood: No azotemia occurred after intraperitoneal injection of blood.

(c) Effect of Iron: To rule out the action of the iron in the hemoglobin, 2 dogs were each given 1 Gm. of iron by a stomach tube in the form of 10 per cent iron ammonium citrate (1 Gm. of iron is the amount normally present in 1,000 cc. of blood). No azotemia resulted.

(d) Relative Effect of Cells and Plasma: In an attempt to find what element in the blood caused the rise, 5 dogs were given beef plasma by a stomach tube in the first series of experiments and in the second series of experiments 5 dogs were given beef cells in the same manner. In all 10 experiments blood samples were taken every day at 2 a. m., 8 a. m., 12 m., 4 p. m. and 8 p. m., one day before giving the substance to be tested and for at least two days afterward. In all instances the dogs given cells showed a much more marked elevation of the urea nitrogen level of the blood than did the plasma-fed dogs. A typical curve is shown in chart 2. That the cells rather than the plasma are the active principle in producing this type of azotemia was reported first by Chunn³⁷ (1940)

36. Chunn, C. F., and Harkins, H. N.: Alimentary Azotemia Due to Whole Blood Absorption from the Gastrointestinal Tract, *Proc. Soc. Exper. Biol. & Med.* 45:569-571 (Nov.) 1940; Experimental Studies on Alimentary Azotemia: I. Role of Blood Absorption from the Gastrointestinal Tract, *Surgery* 9:695-705 (May) 1941; Alimentary Azotemia: A Clinical Syndrome Occurring as a Part of the Bleeding Peptic Ulcer Complex, *Am. J. M. Sc.* 201:745-749 (May) 1941.

37. Chunn, C. F.: Azotemia Following Intragastric Administration of Blood: Studies on Experimental Animals, Thesis, University of Michigan Graduate School, May 1940.

and later by Harkins³⁸ (1940) and by Boals, Chunn and Harkins³⁹ (1940). In a yet later paper, Yuile and Hawkins¹² (1941) reported independent data confirming this conclusion.

(e) Effect of Hemoglobin: Administration of a pure hemoglobin solution to 2 dogs produced a rise in blood urea nitrogen comparable to that produced by cells alone (table 2).

(f) Effect of Protein: Two dogs were given a single large protein meal consisting of casein and ground beef. The first dog received 83 Gm. of protein and the second 175 Gm. A marked rise in blood urea nitrogen occurred (table 3). That the protein in the cellular hemoglobin is the

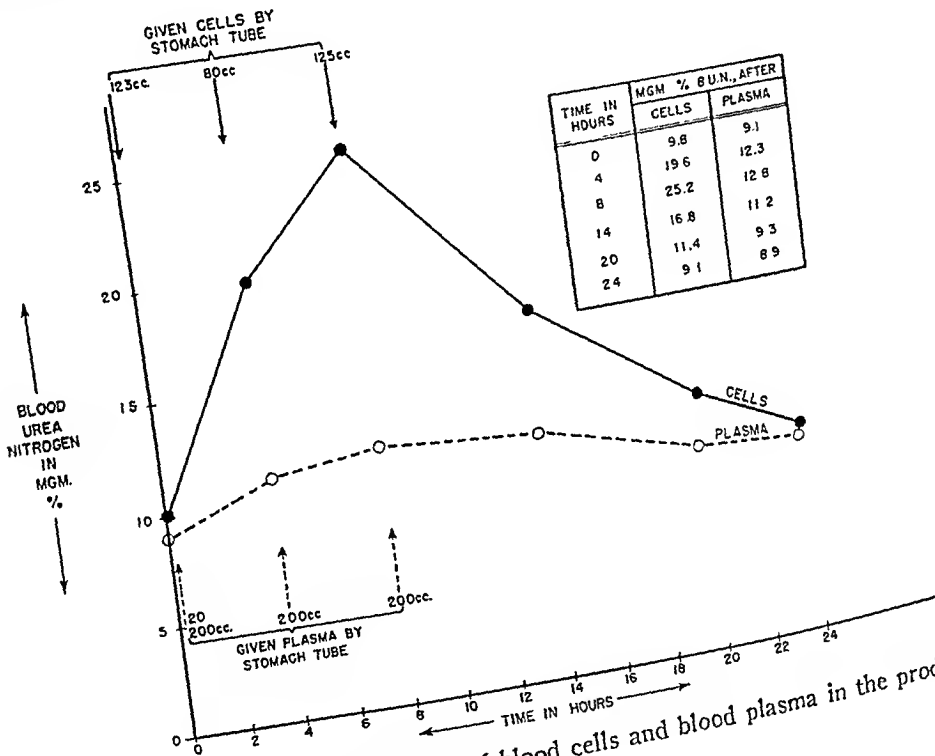


Chart 2.—Comparative effects of blood cells and blood plasma in the production of alimentary azotemia in dogs.

active element is corroborated by the results of Yuile and Hawkins¹² (1941). They showed in an excellent presentation that the rise in the urea nitrogen of the blood after the injection of various substances is quantitatively proportional to the protein content of these substances.

38. Harkins, H. N., in discussion on Schiff, L.; Stevens, R. J., and Moss, H. K.: Prognostic Significance of the Blood Urea Nitrogen Following Hematemesis and Melena, read at the Section on Gastroenterology of the American Medical Association, New York, June 12, 1940.
39. Boals, R. T.; Chunn, C. F., and Harkins, H. N.: Alimentary Azotemia: A Part of the Bleeding Peptic Ulcer Complex; Clinical and Experimental Studies. Program Meet. Cent. Soc. Clin. Research 13:26, 1940.

(g) Effect of the Level in the Intestinal Tract at Which the Blood Is Given: The only observations on the effect of the level in the intestinal tract at which the blood is given prior to our own are those of Schiff and associates⁴⁰ (1939), who observed human beings. They fed blood into the fasting stomach through a Rehfuß tube and into the jejunum or the upper part of the ileum and the colon through a Miller-Abbott tube. The maximum increase in the blood urea nitrogen was greater when the blood was introduced into the jejunum or the upper part of the ileum. After injection of blood into the colon, no appreciable

TABLE 2.—Effect of Hemoglobin in the Production of Alimentary Azotemia in Dogs

Time (Hr.)	Blood Urea Nitrogen (Mg. per 100 Cc.) After Oral Administration of Hemoglobin	
	Dog 1	Dog 2
	(60 Gm. Hemoglobin at 2 Hr.; 60 Gm. Hemoglobin at 6 Hr.)	(30 Gm. Hemoglobin at 2 Hr.; 30 Gm. Hemoglobin at 6 Hr.)
0.....	15.1	16.8
4.....	32.7	24.3
8.....	41.0	33.4
12.....	44.4	34.6
23.....	21.5	20.1
28.....	18.2	15.1

TABLE 3.—Effect of Protein in the Production of Alimentary Azotemia in Dogs

Time (Hr.)	Blood Urea Nitrogen (Mg. per 100 Cc.) After Oral Administration of Protein	
	Dog 1	Dog 2
	(175 Gm. Protein at 3 Hr.)	(83 Gm. Protein at 3 Hr.)
0.....	15.6	16.3
4.....	23.4	17.3
8.....	42.0	34.1
14.....	40.9	29.4
20.....	21.0	20.3
24.....	14.9	16.5
28.....	11.6	15.9

rise occurred. In clinical cases of bleeding into the colon, these authors observed no rise in the urea nitrogen of the blood. We performed 10 experiments on 4 dogs. Two of the dogs had jejunostomy of the Maydl⁴⁰ type 2 feet (61 cm.) below the ligament of Treitz, and the other 2 had an ileostomy of the Mann-Bollman⁴¹ type 8 inches (20 cm.)

40. Maydl, cited by Markowitz, J.: Textbook of Experimental Surgery, Baltimore, William Wood & Company, 1937.

41. Mann, F. C., and Bollman, J. L.: A Method for Making a Satisfactory Fistula at Any Level of the Gastro-Intestinal Tract, *Ann. Surg.* **93**:794-797 (March) 1931.

proximal to the ileocecal valve. Blood or blood cells were introduced by a tube into the enterostomy openings. The effect of intrajejunal feeding was almost as marked as that of blood given by a stomach tube, while similar amounts of blood injected into the lower part of the ileum produced little effect. Azotemia seems to result, then, only from presence of blood in the upper intestinal tract.

(h) Role of the Liver: It is well known that the liver plays a major role in the formation of urea. In agreement with this is the clinical observation of Stadie and Van Slyke⁴² that in cases of acute yellow atrophy of the liver, the blood urea values are low. Blood was given by tube in the usual manner to dogs with Eck fistulas and reverse Eck fistulas and after hepatectomy. In chart 3 it is shown that practically no

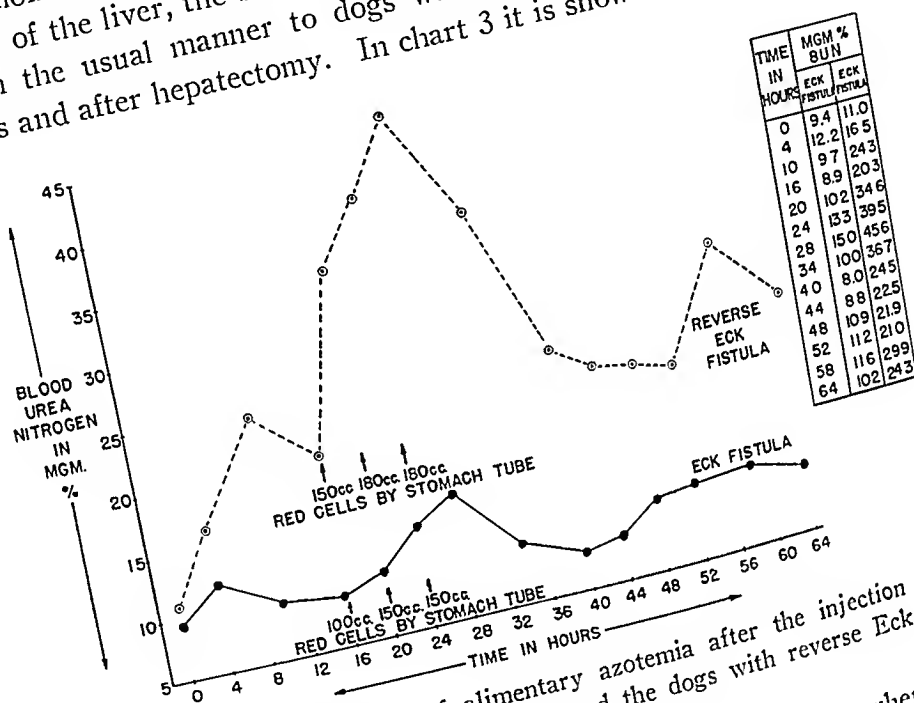


Chart 3.—Relative amount of alimentary azotemia after the injection of red blood cells into the dogs with Eck fistula and the dogs with reverse Eck fistula.

azotemia resulted in an animal with a typical Eck fistula, whereas the rise in the urea nitrogen of the blood in the animal with the reverse Eck fistula was actually greater than in the average animal with normal portal circulation. In chart 4 it is seen that despite the intraduodenal injection of blood into a liverless animal, the urea nitrogen level of the blood fell. It is of interest that the plasma prothrombin level fell at the same time.

ALIMENTARY AZOTEMIA—A PROPOSED NEW TERM

The name "azotemia" has been applied to this syndrome since the time of Sanguinetti's first description in 1933. The word "azotemia"

42. Stadie and Van Slyke, cited by Christiansen.^{3c}

denotes the presence of urea or of other nitrogenous bodies in the blood in abnormal amounts. Arguing from analogy to the commonly used term "alimentary hyperglycemia," it seems logical that the urea syndrome be termed "alimentary azotemia." The mechanism in both is the same, and the adjective differentiates both conditions from similar ones of different causation. Use of the designation "extrarenal azotemia" is not definitive enough. "Alimentary azotemia" means the azotemia due to ingestion of excessive proteins. In bleeding peptic ulcer it is probable that a large share of the resultant azotemia is alimentary azotemia due to ingestion of blood proteins; part of it may be due to other types of extrarenal azotemia, while in some instances actual renal azotemia may be a contributory factor.

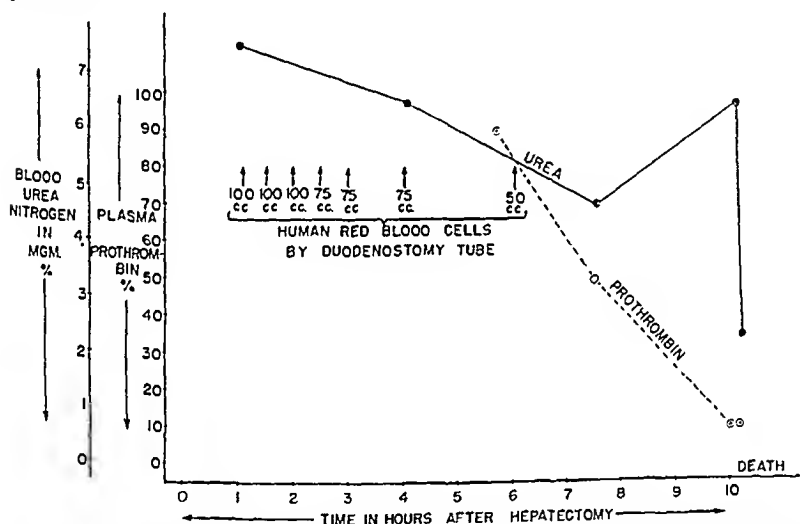


Chart 4.—Effects of the administration of red blood cells on the urea nitrogen content of the blood and the plasma prothrombin level after total hepatectomy.

CONCLUSIONS AND SUMMARY

Alimentary azotemia occurs in cases of massive hemorrhage into the upper intestinal tract, a common example of which is bleeding peptic ulcer.

The degree of azotemia is of considerable prognostic significance; high blood urea nitrogen values are associated with a high mortality rate. Persistent azotemia tends to indicate persistent bleeding in most instances rather than serious hepatic or renal damage, and therapeutic indications are calculated accordingly.

In cases of hematemesis and melena, azotemia is essentially caused by absorption of the red cells rather than of the plasma fraction of the lost blood. This is accounted for by the high protein content of the cell hemoglobin.

In our experiments starvation, dehydration, bleeding, anemia and shock did not play a major part in the production of azotemia.

Presence of the liver with an intact portal circulation is essential for the occurrence of alimentary azotemia.

The term "alimentary azotemia" is proposed for the syndrome of increased blood urea nitrogen following alimentary absorption of large amounts of digested protein. This condition occurs clinically most often in patients with bleeding peptic ulcer.

ABSTRACT OF DISCUSSION

DR. D. H. KAUMP, Detroit: Parsons and I have shown that the rise in blood urea is dependent to a large extent on the amount of blood given to the experimental animal. It is therefore logical to assume that a continued rise in urea values of the blood indicates a continuously bleeding process and consequently presages the death of the patient.

Repeated estimations of blood urea for patients with bleeding syndromes are of vastly greater value than single determinations.

As to the cause of alimentary azotemia, Parsons and I were unable to find evidence of renal failure in our experimental animals. However, in the human being with damaged kidneys, one might expect a slight acceleration or prolongation in this rise.

I doubt whether shock is of any particular consequence in relation to alimentary azotemia because in patients with bleeding peptic ulcers the shock element is not as great as one might expect from the degree of urea rise. With adequate treatment, the urea values fall to normal but much more slowly than the patient recovers from shock.

Drs. Harkins, Chunn and Boals observed a less marked urea rise in animals adequately hydrated by the administration of physiologic solution of sodium chloride and of dextrose; that is equally true in human beings because in patients with alimentary azotemia there is a prompt fall in the urea values with the administration of fluids. Consequently, dehydration probably does play some part. I doubt whether the sodium chloride in the fluids contributes much to this recovery, primarily because the urea values fall to normal long before the blood and urinary chlorides reach normal levels.

DR. LEON SCHIFF, Cincinnati: This work is particularly gratifying as it confirms a number of observations made by my associates and me in human beings.

While a number of factors, particularly renal, may play a role in the causation of azotemia in a given patient with hematemesis or melena, the essential factor is the presence of blood in the upper intestinal tract.* Everything else being equal, the degree of azotemia is dependent on the amount of this blood and the unit of time in which it appears.

The evidence in one of the experiments convinced my associates and me that it was the digestion of the blood protein in the intestinal tract and the absorption of these digestive products which accounted for the azotemia in question.

Azotemia which follows hematemesis in patients with hepatic cirrhosis is of even greater prognostic import than that seen in patients with bleeding peptic ulcer; that which occurs in the presence of obvious nephritis is of less import. Over half the patients who have come to my notice with bleeding esophageal varices and with a concentration of urea nitrogen in the blood of 30 mg per 100

hundred cubic centimeters or more have died shortly after the onset of hemorrhage. This may be explained by the fact that the degree of azotemia was not a true expression of the extent of the loss of blood because the liver's ability to produce urea nitrogen was impaired. When nephritis is present the degree of azotemia may be exaggerated as the result of impaired kidney function.

Occasionally there is no azotemia after severe hematemesis, even within a day or two after hemorrhage. This may be explained by (1) external loss of most of the blood through vomiting, (2) intestinal hypermotility, sometimes induced by a cathartic taken immediately after hematemesis (as occurred in 2 of our cases), (3) renal excretion of urea exceeding the production of urea and (4) factors as yet unknown.

DR. WALTER L. PALMER, Chicago: The authors are to be congratulated on devising the appropriate term "alimentary azotemia."

They and others have shown the preeminent role of increased blood in the intestine as a cause of alimentary azotemia. A priori, one would think that renal function would play a considerable role in causing the elevation of the level of the urea nitrogen of the blood. When the blood pressure suddenly drops from 140 or 130 to 90 or 80, one would think there might be sufficient decrease in the renal blood flow to bring about significant reduction in renal function. However, this does not seem to happen; the present authors and other workers have shown that normal or almost normal renal function is present under such circumstances. In the last 2 patients whom I have seen with massive hemorrhage from peptic ulcer and marked increase of the blood urea nitrogen the urea clearance test of renal function yielded results within normal limits.

The prognostic value of the elevated level of the urea nitrogen of the blood does seem to be definitely established. In the 1 case that has come to my attention in the last year or two in which a patient died the patient had the highest blood urea nitrogen I can recall having seen. Of course, the essential thing in cases of massive hemorrhage is not the amount of blood in the intestine but the amount of blood left in the cardiovascular system. The physician should be able by means of continued or frequent blood transfusions to compensate for the blood lost in the intestines and in some way or other bring about cessation of the hemorrhage and eventual recovery. However, this does not seem always to be possible. The elevation of the level of the blood urea nitrogen is helpful in enabling us to estimate the amount of blood lost.

DR. HENRY N. HARKINS, Detroit: I agree that persistent elevation of the level of the urea nitrogen of the blood indicates persistent bleeding. It should be emphasized that conclusions drawn from any experimental work have to be applied to human beings with caution, because in human beings other factors may be of importance. There are two reasons why human patients are apt to have complicating conditions more often than dogs. First, patients who have peptic ulcer with persistent bleeding are apt also to have arteriosclerosis. In fact, these patients have arteriosclerosis in a higher proportion than the average population. That is why the ulcer tends to continue bleeding. Second, many patients with peptic ulcer have been treated with alkalis over a long period, and this may have impaired their renal function to some extent.

There was not time to mention that Dr. Schiff and co-workers were the first to point out that the intestinal level of bleeding was of importance, but the findings in our experiments with animals agree with their data from patients that only blood in the upper intestinal tract will cause this increase in the urea nitrogen of the blood.

However, if urea itself is put into the intestine at two levels, the urea nitrogen becomes increased in both instances. This indicates that the urea is absorbed at both levels. Why absorption of blood low down in the intestinal tract does not cause a rise in the urea nitrogen is not explainable at present.

I believe that among others Dr. M. G. Wohl once said that this syndrome cannot be due to absorption, because the phenomenon does not occur in cases of ectopic pregnancy. My associates and I have placed blood within the peritoneum in animals and have observed that the urea nitrogen of the blood did not increase. It is probable that even if the blood is absorbed from the peritoneal cavity, the absorption is so slow in comparison with that which occurs from the intestine that no azotemia results.

Dr. Schiff, Dr. Kaump and others have emphasized the importance of frequent readings both for experimental animals and for patients. In many previous observations these elevations have been missed because the readings were not frequent enough. I can vouch for the importance of frequent determinations from personal experience, because in our experiments Dr. Chunn and I had to obtain readings at all different hours of the night; in fact, since the animals were usually fed in the daytime, the night readings were those which showed the highest elevation.

There has been a prejudice against surgical intervention in cases in which the urea nitrogen level of the blood is elevated. I think the work presented emphasizes that this may not always be logical and that actually the presence of a rise in the urea nitrogen of the blood may be an indication for operation, other things being equal, rather than a contraindication.

HYDATID DISEASE (HYDATIDOSIS)

HYDATID CYST OF THE LUNG

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After the liver the lung is the most frequent site of the localization of hydatid cysts. Those hexacanth embryos which are able to pass through the hepatic filter cross the right side of the heart and reach their second filter, the lung; here they can attach themselves and develop into hydatid cysts.

Hydatid cysts of the lung can be central or peripheric. The latter, through their ever increasing growth, can come into contact with the pleura. Whether central or peripheric, a pulmonary hydatid cyst may empty into a bronchus and be expelled through a hydatid vomica.

Sometimes, when the entire parasite (fluid and membranes) is expelled, spontaneous healing of the disease occurs. If only the fluid is eliminated, the membranes will remain in the adventitial cavity where the retraction of the cavity's walls and the narrowness of the bronchial opening make the expulsion of the membrane almost impossible (incarcerated membrane).

In contrast with the adventitia of a cyst of the liver, that of a cyst of the lung has only two layers: the inner stratum, thin and composed of connective tissue, and a thicker outer one, formed by atelectatic lung tissue which has recuperative powers (false adventitia).

From the clinical point of view, the hydatid cysts of the lung may be divided into ordinary and complicated cysts.

The former are always latent and offer no symptoms. Sometimes there is a slight dry cough with slight hemoptysis; pain is exceptional, unless the cyst is in contact with the pleura. In any case, a cough, slight hemoptysis and pain may suggest the presence of a disorder of the lung but never point to any definite diagnosis.

If there is a cyst of the lung, a roentgen examination of the thorax, indispensable even in the briefest clinical examination of this region, shows a more or less rounded shadow. However, it must be borne

This is the third article on hydatid disease contributed by Dr. Arce at the suggestion of the Chief Editor of the ARCHIVES.

in mind that this shadow, even if the patient has pain, cough and hemoptysis, will never uphold a positive diagnosis.

The signs and symptoms just stated, a good general condition and a positive biologic syndrome (eosinophilia, with the Imaz-Lorentz complement fixation test and the Casoni test of the skin both positive) can secure a probable diagnosis but never an absolute one. The only absolute



Fig. 1.—Roentgen image of the perivesicular pneumonia.

sign is a hydatid vomica (hydatidophthysis) with hydatid membranes, scolices or hooks in the expectorated matter.

On the other hand, complicated hydatid cysts offer positive signs for an absolute diagnosis. As the complications originate in the sphere of the bronchi, it is convenient to stress here the importance of the process by which the cysts open into the bronchi and describe the different degrees to which this takes place.

The bronchial wall having been gnawed by the eccentric growth of the parasite, the outer aspect of the latter comes into contact with the

lumen of the bronchus. One or more deep breaths or fits of coughing may bring a small amount of air in between the parasite's membrane and its adventitia. This can be detected by means of roentgenograms; the air appears in the shape of a cap and gives rise to what is called the "perivesicular pneumonia" (fig. 1). This typical roentgen picture allows a definite and absolute diagnosis.

At a later stage, the membrane is torn, and part of the fluid is expelled and replaced by air. The latter finds its way in between the



Fig. 2.—Roentgen image of the double arch.

adventitia and the membrane and also between the membrane and the remaining fluid. On roentgen examination, the membrane shows two air chambers, the upper one in contact with the adventitia and the lower one in contact with the fluid level. This is the "double arch image," described by my co-worker Prof. Oscar Ivanissevich (fig. 2).

The cystic membrane may become torn or totally disintegrated, and the whole or just part of it may float on the remaining fluid. The roentgenographic image shows an air cap on the upper section and a dull, movable and horizontal shadow on the lower (the hydatid fluid).

Between the two a lighter shadow can be seen; it is the cystic membrane or one of its fragments floating like a water flower on the fluid. It is the "water flower sign" (fig. 3).

To form the pictures just described, the presence of a part or the whole of the hydatid fluid is absolutely necessary. However, it may

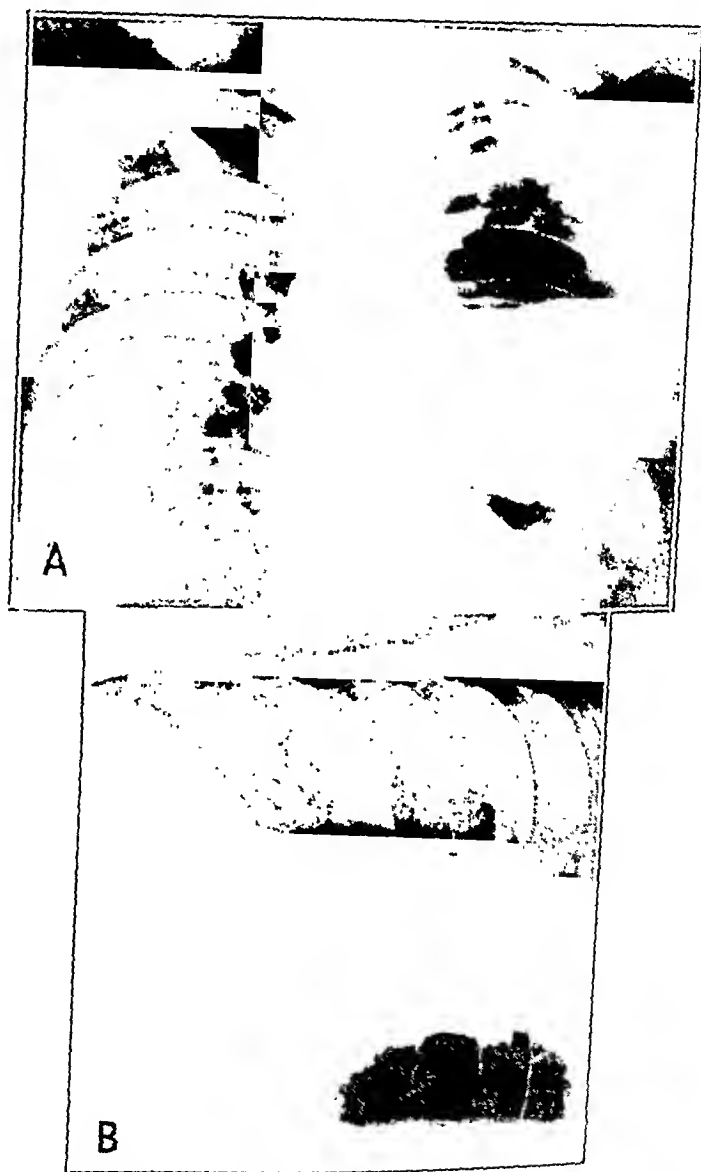


Fig. 3.—*A*, Roentgen image of the water flower taken from a standing position; *B*, from a recumbent sign position.

happen that all of it has been expelled and only the membrane remains. This is what I called before an incarcerated membrane. The frontal roentgenographic image of this is almost circular (though obviously it will be less opaque than the image of an uncomplicated hydatid cyst), but the lateral one is polygonal (fig. 4). The contrast between the two

images may be due to the uniform retractibility of the membrane in the frontal direction (round frontal image) but rather difficult retractibility in the anteroposterior direction on account of the membrane's connections with the bronchi (it must be remembered that the bronchial divisions take place only in the anteroposterior direction). Although these reasons are not absolute, the fact remains that the concomitance of both images in a patient allows a positive clinical diagnosis.

The surgical treatment of hydatid cyst of the lung consists of two operative stages, thoracotomy and treatment of the cyst.



Fig. 4.—*A*, frontal roentgen image of an incarcerated membrane, showing the circular borders; *B*, lateral image, showing the polygonal borders.

TECHNIC OF TREATMENT

A. Thoracotomy.—The opening of the thorax differs according to the presence or absence of pleural adhesions.

1. If confirmed adhesions have placed the lung in contact with the thoracic wall at the level of the cyst, the operation becomes a simple one. Under local anesthesia, 10 cm. of the lowest rib situated within the zone of the adhesions is resected. Once the pleura is exposed, the cyst is opened (pleuropneumonotomy) and its contents removed.

However, the surgeon should never trust that all adhesions are sufficiently numerous and solid to allow this easy operation. It is therefore advisable to proceed with the utmost care once the rib has been removed.

First of all, the surgeon should determine whether the lung slides under the parietal pleura or not. If there are no adhesions, this motion can be easily elicited by asking the patient to breathe in deeply.

If the lung is not seen to move or even if a process of adhesive pleuritis in the exposed zone is observed, the surgeon should go slowly, layer by layer, until he is certain he has reached the lung tissue. If there are no adhesions present and the parietal pleura has been cut, the shiny inner pleural layer (visceral pleura) can be clearly seen forming an independent structure, even when no air goes in and the lung does not become retracted. This may occur in cases in which there is a normal pleura, cases in which large cysts are in contact with the thoracic wall or in which there are only loose adhesions.

If pleural adhesions are present, the roentgen examination, which should be carried out by the surgeon himself in all cases of thoracic disturbance, will show the zone in which the operation should be performed. If there are lateral adhesions, the shadow comes in contact with the thoracic wall when the patient is examined from the front or from the back; this situation calls for lateral thoracotomy between both axillary lines. If there are frontal or posterior adhesions, the shadow comes in contact with the thorax in the front or back only when the patient is examined in profile or in oblique positions. Such a picture indicates either anterior or posterior thoracotomy, according to the type of adhesions.

In short, there is only one way of making absolutely certain whether or not there are adhesions, and that is by producing an artificial pneumothorax. This method is also useful when the roentgenogram shows one or more unreliable shadows, as it will clarify the diagnosis. If the contact between the lung and the thorax persists in spite of the production of a pneumothorax carried out at high positive pleural pressures, there is no doubt whatever about the presence of adhesions.

I have already spoken about the great care that should be taken before operation to avoid being met with an absence of adhesions or the presence of small or loose ones. If one arrives at this pass, what is to be done? Personally, when I am going to operate with use of a local anesthetic, I have the patient placed under a closed circuit anesthetic apparatus, which is made to work with oxygen alone when the need arrives. Moderate pressure on the oxygen-containing elastic bag is enough to increase the pressure inside the lung and thus bring both pleural layers together. The operation is performed as if the patient were under inhalation anesthesia with hyperpressure (*baronarcose*).

In the absence of a closed circuit anesthetic apparatus, it is better to fix the lung to the thoracic wall before opening the pleura. This is done with two or more stitches (*harpooning*) which cross the soft structures of both the costal wall and the lung. The stitches should be

placed well outside the zone in which the cyst is supposed to be, so as to prevent the needle opening the cyst before it is time to do so.

Of the foregoing two procedures, my preference lies with the first.

Once the cyst has been opened and its contents removed, if there are no adhesions or if those present are found unsatisfactory, the edges of the adventitia are attached to those of the structures under the skin. This is carried out by means of loose stitches, preferably crossing the intercostal muscles or, in defect of these, the deepest muscular layer of the thoracic wall.

Adhesions are the rule, or at least occur frequently, in connection with complicated cysts, particularly those which have become septic to the point of being true hydatid abscesses. These adhesions, sequelae of the pulmonary and pleural inflammation caused by infection of the cyst's neighboring structures, lead to the formation of a pleural symphysis. This fortunate defensive process allows the performance of pneumotomy and evacuation of the cyst's contents by a simple operation.

2. In the absence of adhesions, four procedures can be carried out: (a) the creation of artificial adhesions; (b) the production of pulmonary hyperpressure with or without inhalation anesthesia; (c) the harpooning method according to Posadas' technique; (d) the preoperative production of an artificial pneumothorax (Aree's method).

The first three maintain the contact between the lung and the thoracic wall to avoid a pneumothorax; the last method, on the contrary, causes a pneumothorax to be present.

(a) The method of creating artificial adhesions (sometimes called the method of Lamas and Mondino, after the two Uruguayan surgeons who devised it) consists in localizing the cyst in detail by roentgenographic, tomographic, and other methods, removing 4 to 6 inches (10 to 15 cm.) of the rib nearest the tumor and packing the wound with plain or iodoform gauze. The packing, through compression and irritation of the zone of the pleural membranes above the site of the tumor, gives rise to a process of plastic adhesive pleuritis. The packing is changed if necessary once or oftener, and after two weeks (sometimes three) strong adhesions will have been formed. These will enable the surgeon to open and empty the cyst without risk of the development of an operative pneumothorax or of contamination of the pleural cavity.

(b) The method of pulmonary hyperpressure may or may not be combined with inhalation anesthesia (*baronarcose*). It requires the application over the patient's face of an apparatus which will allow the closing of the respiratory circuit and the increase of the gases contained therein. With hyperpressure ranging between 2 and 7 mm. of mercury, the pleura can be opened and the lung exposed without fear that the latter may become retracted as in those cases in which the pleural cavity is opened in the absence of adhesions.

Compared with the first, this method offers the advantage of allowing exploration of the lung and exact localization of the cyst. All exploratory procedures must be carried out with a small degree of hyperpressure, so that the surgeon may introduce his hand into the pleural cavity and feel the lung until the cyst is localized exactly. Then the part of the lung containing the cyst is drawn to the operative wound. The hyperpressure is increased at this moment so as to establish an intimate contact between both pleural membranes, thus avoiding the possibility of blood or cystic contents entering the pleural cavity when the cyst is opened.

(c) My teacher Posadas first published a description of his harpooning method in 1898. An osteomusculocutaneous flap containing two ribs is made over the site where the cyst has been localized by roentgen examination. (This localization should be carried out with the utmost care so that perforation of the cyst may be avoided at the next stage.) Once the parietal pleura has been exposed, both pleural membranes and the lung are united by two untied loose stitches of thick catgut (made with a Hagedorn needle). These stitches, situated above and below the cyst, penetrate the lung tissue and afterward leave it at a certain distance from the point of penetration. The loose ends of the catgut are maintained tense to keep the lung well in contact with the costal wall, thus avoiding the formation of a sudden pneumothorax at the moment of the pneumonotomy and evacuation of the cyst.

This method can be connected with the operative pneumothorax because, though Posadas carried it out in order to avoid the effects of a pneumothorax, it is impossible to avoid with it a slight tearing of the parietal pleura and consequent penetration of some air into the pleural cavity with the formation of a small operative pneumothorax.

Other surgeons pay no heed to this preliminary harpooning method. They simply open the parietal pleura and allow air to penetrate in a slow way (slow operative pneumothorax of the French school). Later, with the hand or instruments they draw the pulmonary lobe wherein the cyst lies to the operative wound and finally perform the pneumonotomy and evacuation of the cyst.

(d) Since I propounded the method of preliminary pneumothorax in 1919,¹ I use it exclusively. The technic of this method is described in an article of mine on thoracotomy with free pleura, published in 1926.² The preliminary pneumothorax produces atelectasis of the lung to the point that this organ becomes retracted around the cyst and against the hilus. On account of this retraction, it is better to reach

1. Arce, J.: Preliminary Pneumothorax in Lung Surgery, *Surg., Gynec. & Obst.* **36**:687 (May) 1923.

2. Arce, J.: The Technique of Thoracotomy with Free Pleura, *Surg., Gynec. & Obst.* **33**:355 (Sept.) 1926.

the cyst through a more or less high anterior thoracotomy (in the region of the second to the sixth rib, according to the site of the cyst). Yet it happens sometimes that either the cyst or the lung has become partly adherent to the costal wall (axillary zone or posterior zone) so that the pneumothorax does not give rise to the total retraction of the lung. In such a case it is advisable to perform the thoracotomy according to the information provided by the roentgen examination, which the surgeon should carry out personally the day before the operation.

Once the pleura is opened, the surgeon explores the hemithorax, localizes the cyst or cysts and with his hand draws the parasite-infected lobe to the operative wound for the performance of the pneumonotomy and evacuation of the cyst. The lung should be treated gently, and any pulling ought to be done with the utmost care, in order not to diminish the advantages offered by the preliminary pneumothorax. It is therefore wise to avoid the use of instruments when drawing the tumor to the operative wound. The bare hand will not injure the lung tissue, and any reflexes provoked will be at a minimum.

It has been stated, purely from a theoretic standpoint, that a preliminary pneumothorax handicaps traction of the tumor toward the operative wound. My wide experience in this connection has taught me that such is not the case. If, owing to adhesions, the lung has not become totally retracted and the surgeon endeavors to draw it to the opposite side because of a faulty thoracotomy incision, it is perfectly obvious that he will find this task most difficult. Yet it must be borne in mind that although as a rule this method calls for an anterior incision, there are, as I have already stated, exceptions which can and must be foreseen by a simple roentgen examination. This examination must be carried out by the surgeon himself on the day before the operation. If there are still any doubts, a tomographic examination will definitely clear the picture.

B. *Treatment of the Cyst.*—Whenever possible, it is well to protect the pleural cavity before opening the lung. This should be done throughout the wound by means of sterile gauze towels soaked in warm solution of sodium chloride. This measure is indispensable when the operation is performed under hyperpressure or with a preliminary pneumothorax.

1. How should the cyst be opened? The first step is to make an exploratory puncture for the purpose of verifying the diagnosis. Complicated cysts and those which have emptied themselves into a bronchus give no response to this procedure, a fact which is of no importance when the patient's clinical record is borne in mind. The introduction of the needle into the lung and its contact with the pathologic process provide a peculiar tactile sensation which is easier to perceive than to describe and is totally different from that in the case of a solid tumor.

If the puncture gives origin to a flow of clear fluid, this should be drawn out gently and slowly, the syringe being changed as often as necessary. During this procedure, the point of the needle remains in the cavity of the cyst, while the outer part is plugged by an assistant every time a syringe full of fluid is withdrawn. In order to avoid having to change the syringe more than once or twice, I usually replace the one used for exploratory purposes by another with a capacity of 100 cc.

I advocate the gentle and slow method of drawing out the fluid. Finochietto propounds instead the abrupt and rapid drawing out of the fluid by means of a trocar attached to a flask in which a vacuum has previously been made. I use this procedure in operating on a cyst of the liver and large cysts of other organs but never in operating on a cyst of the lung. I am firmly convinced that the abrupt method offers certain inconveniences which do not arise with the slow and gentle one.

When the cyst has been totally emptied, the needle is removed and in its place an incision (pneumonotomy) is made. This incision should not be too long but should reach the cavity of the cyst. Then the edges of this incision are held open while the surgeon, with a flexible clamp or a heart forceps, removes the hydatid membrane and ends this stage by drawing off any remaining fluid with gauze swabs. All these steps should be carried out as gently as possible, particularly when operating with only the field under anesthesia. In this case the contact of the swabs (or of any foreign body, for that matter) with the small bronchi open on the adventitial membrane gives rise to fits of coughing and other disturbances in the patient. I have made a habit of using the speculum procedure after the fashion described in discussing cysts of the liver when inspecting and cleaning the walls of the cavity of medium-sized and large cysts.

When I am faced with an incarcerated membrane after having both observed an absence of fluid by means of the exploratory puncture and performed the pneumonotomy, I remove the membrane, which is in a varied condition of disintegration, and cleanse the cavity thoroughly.

In operating on hydatid abscess, it is best to withdraw the contents with a needle of large diameter or with the smallest trocar of the electric suction apparatus. When the latter is employed, care should be taken to have only enough pressure to run the pus into the suction flask. These precautions, together with the protecting towels soaked in warm solution of sodium chloride, will undoubtedly preserve the pleural cavity from contamination. Once the suction process is over, the pneumonotomy and the cleansing of the cavity are carried out as in the other cases.

2. What is to be done with the adventitial cavity after the parasite has been removed and the cavity cleansed? The adventitial pouch of septic cysts and, generally speaking, of all complicated cysts must be marsupialized and drained. This is done by suturing the edges of the incision in the lung to those of the operative wound. This suture includes not only the parietal pleura but also the intercostal muscles and the endothoracic fascia; this provides the marsupialization with greater support and strength. If these structures are found to be weak, the surgeon should not hesitate to include in the suture the deepest layers of the thoracic muscles.

If the cyst is aseptic, Posadas' method, that is, suture without drainage, may be employed, but I perform it only in cases in which there are small or multiple cysts. Experience has taught me that although marsupialization of a cyst of the lung does not offer the same inconveniences as that of a cyst of the liver, the closing without drainage may engender some difficulties. These usually are due to the opening of one or more small bronchi into the adventitial pouch; this may give rise to an infection which may and often does develop into a true post-operative abscess of the lung.

In a case in which there was a conglomeration of cysts in a lingula of the anterior border of the right lung, I partly resected this lingula. This case was undoubtedly exceptional, but under similar circumstances there should be no objection to a lobectomy, especially if the entire lobe or the greater part of it is affected by the disease.

HYDATID CYST OF THE KIDNEY

The elimination through the urine of daughter vesicles, proliferous vesicles, scolices or hooks definitely confirms the diagnosis in those cases in which a hydatid cyst of the kidney is suspected.

In all other cases a positive diagnosis is impossible, but with a good general condition, a hydatid cyst of the kidney might be suspected before a tumor of long evolution. This possibility may be further strengthened by a positive biologic syndrome.

If the tumor protrudes in the renal pelvis, the groove which appears in the pyelogram usually takes the shape of a segment of a sphere.

In the great majority of cases, the diagnosis is made on the operating table.

The long evolution of the hydatid cyst of the kidney, together with the fact that it has no bearing on the patient's general condition, explains why this disease in the great majority of cases is discovered only when the greater part of the organ has already been destroyed. Then there is no alternative but to perform a nephrectomy.

Yet sometimes the surgeon finds small or medium-sized cysts which have not affected the entire organ. If these are localized on the lower

end of the kidney and do not interfere with the renal pelvis, their total removal is possible by a partial resection in the shape of a triangle, thus avoiding a total nephrectomy. Of 13 cases observed at the clinic of the Surgical Institute it was possible to use this procedure in only 1.

A cyst of the kidney should never be marsupialized. This technic should be avoided, unless it is absolutely indispensable because of indications of a general character, such as the condition of the patient or that of the other kidney.

HYDATID CYST OF THE SPLEEN

Hydatid cyst of the spleen is even more difficult to diagnose than that of the kidney. Only the increase in size of the organ or the presence of a large tumor in the left hypochondrium of a patient coming from a zone of infection may suggest the disease.

The best treatment for the splenic cyst is splenectomy. Marsupialization is usually followed by long-standing fistula, which leads to amyloid degeneration of the spleen and later to that of the liver and kidneys.

HYDATID CYST OF THE BRAIN

It is almost impossible to diagnose hydatid cyst of the brain. Obviously, the clinical signs derived from irritation or compression of a zone containing important functional centers may lead to the diagnosis of a tumor of the brain but will never point out its parasitic nature. If the cyst lies in a silent zone, it may reach a great size without showing any outward signs except for the general ones of cranial hypertension in the late stages. At any rate, a ventriculogram will generally allow exact localization of the tumor and point out the only possible therapeutic course, surgical intervention.

In children the hydatid cyst is often seen to come into contact with the endocranium. It is often the cause of wasting and thinning of the bones of the vault, which can sometimes be felt with the fingers and gives a sensation of parchment (parchment sensation).

The operation consists of an exploratory craniotomy and exposure of the affected zone of the brain. If the tumor has reached the cortex, the adventitia is cut at an avascular point and the hydatid punctured. After the fluid has been evacuated, the germinative membrane is carefully extracted through the hole in the adventitia, pains being taken that it is not torn or fragmented lest any fluid fall on the operative field.

All these procedures should be carried out with the utmost care, as the adventitia is so thin that some authors have even denied its existence. It is formed by scanty connective tissue from the vessels and by neuroglial elements and therefore these appear in the form of a veil-like membrane surrounding the hydatid cyst.

The operation ends with the suture of the dura mater and the replacement of the flap of scalp and bone, without leaving drainage.

If the tumor does not appear on the surface of the brain, it must be discovered by an exploratory puncture followed by suction of all the hydatid fluid. A small incision on the cortex will later permit removal of the parasitic membrane.

SECONDARY HYDATIDOSIS

The formation of hydatid cysts may be due to other causes than ova of *Taenia echinococcus* in the intestine of man. Scolices contained in a ruptured human hydatid cyst may attach themselves in any part of the human body and give rise to cysts identical with those from which they came. This process is called secondary hydatidosis. If the ruptured cyst empties its contents into a blood vessel, the blood stream carries the scolices to the organ to which they become attached. This gives origin to what is called metastatic secondary hydatidosis.

The most frequently occurring form of direct secondary hydatidosis, that without intervention of the blood stream, is peritoneal hydatidosis. The frequency is easily understood if it is remembered that in 70 per cent of the cases hydatid cysts occur in the liver and that the surface of this organ in contact with the peritoneum is indeed large. Besides, clinical and pathologic figures show that rupture of cysts in the liver happens frequently.

Some of the scolices which fall into the peritoneal cavity die, but those which become grafted undergo vesicular transformation. Through this change the scolices, instead of developing into taeniae (as they would have, had they been in a dog's intestine), turn into new hydatids equal to those formed at the expense of hexacanth embryos.

Secondary peritoneal hydatidosis can adopt two anatomic forms: the miliary hydatidosis of the peritoneum and the multiple hydatidosis. In the first instance, numberless scolices become attached to the serous membrane but do not undergo the vesicular transformation; they may resemble miliary tuberculosis. In the second form the scolices undergo the vesicular transformation and give rise to the formation of numerous cysts of variable size. These cysts are spread all over the peritoneal cavity, but especially in the declivitous regions and in the omentum majus.

This last form is often of a serious character, owing to the functional and mechanic disturbances caused by hundreds of cysts. Patients are subjected to countless series of operations to remove the larger ones or those which have undergone complications (septic cysts).

Another form of secondary hydatidosis is that which originates in the lung by the rupture of a cyst and the spread of its contents on the same

lung or the opposite one through the bronchial tree (bronchogenic hydatidosis).

BONE HYDATIDOSIS

The peculiarities offered by hydatidosis of the bones are such that I feel compelled to say a few words about them. As in other structures, the hexacanth embryo that reaches a bone through the blood stream and becomes attached to it undergoes vesicular transformation. However, little by little the hydatid vesicle is faced with true hostility on the part of the lodging structure, which has hard lamellas and lacks elements capable of reacting to the presence of the parasite. This resistance modifies the usual biologic tendency of the parasite. The vesicle finds its free growth hindered by the characteristics of the surrounding tissues. At the same time it is naked, without an adventitia; the walls of the cyst are in direct contact with the lamellæ without any interposing connective tissue. The only elements that react in the presence of the cyst are those of the medulla ossium, and these surround the outer aspect of the chitinous membrane with a practically negligible adventitia.

From these facts are derived the characteristics of bone hydatidosis. Prevented from growing freely, the primary hydatid grows by producing exogenic daughter and granddaughter vesicles; these accumulate side by side until they form a conglomeration of hydatid vesicles capable of invading the entire bone, perforating the substantia compacta and the periosteum and even invading the soft parts. Therefore, bone hydatidosis is not unilocular but multilocular. The lack of an adventitia and the formation of exogenic vesicles which slowly infiltrate and destroy the osseous tissue without the latter attempting to defend itself show that there are no such things as hydatid cysts of bone (the blend of the parasite and the reaction of the host) but only an infiltrating hydatidosis, after the fashion of neoplasms.

Nevertheless, the biologic unity of the disease is still present. The proof of this assertion is the fact that if the bone becomes fractured and one or more hydatid vesicles fall among less hostile structures (muscle, subcutaneous tissue), their original tendencies reappear, and each gives rise to a unilocular hydatid cyst with an adventitia.

Bone hydatidosis is difficult to diagnose. Its evolution is slow and silent. Its presence is often suspected only as a result of the study of a roentgenogram taken after a pathologic fracture has occurred.

The prognosis is serious because of the difficulties of efficient treatment. The only treatment is the resection of the whole affected part, and the surgeon usually ignores the question as to how far this resection must be carried to make the treatment a success. Not long ago I resected one whole humerus of a woman, who fortunately is able to use her arm thanks to an excellent prosthetic apparatus which is now available.

CARCINOMA OF THE UPPER EXTREMITY

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Carcinoma of the upper extremity is not a common disease. Less than 10 per cent of all cutaneous lesions diagnosed as carcinoma occur at this site.¹ Heilman found 207 cases of carcinoma in which an upper or a lower extremity was the site among 2,054 cases of cancer; Broders, 44 cases in 2,000; DeAsis, 132 in 6,766.² In two thirds or more of the 207 cases the carcinoma occurred on an upper extremity. While prog-

TABLE 1.—*Conditions Present Preceding Carcinoma of Hand or Arm in Reported Cases*

	University of Michigan Series of Cases	Mason's Series of Cases	Mason's Collected Cases	DeBell's Series of Cases
Roentgen or radium irradiation.....	2	6	..	2
Trauma.....	2	7	20	} 25
Keratosis.....	10	
Verrucae.....	3	1	..	
Unchanged skin.....	..	2	..	
Condition unknown.....	..	3	..	
Scars other than from burns.....	21	
Scars from burns.....	2	..	19	5
Chronic inflammation.....	12	
Lupus vulgaris.....	1	..	10	1
Arsenical dermatitis.....	1(?)	..	2	

nosis is usually considered good, too frequently such a lesion is overlooked or undertreated.

The etiologic factors were well outlined by Adair,³ who expressed the belief that there are six main types resulting from: (1) changes of old age; (2) exposure to the elements; (3) previous burns; (4) internal medication; (5) prolonged chemical irritation; (6) roentgen or radium irradiation of the skin.

In the University of Michigan series in table 1 carcinomatous change occurring in keratoses was the largest proved etiologic factor.

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1. Mason, M. L.: Carcinoma of the Hand, Arch. Surg. **18**:2107-2158 (May) 1929.

2. Cited by DeBell, P. J., and Stevenson, T. D.: Squamous Cell Epithelioma of the Extremities, Surg., Gynec. & Obst. **63**:222-229, 1936.

3. Adair, F. E.: Epitheliomas of the Hand: Types and Treatment, S. Clin. North America **13**:423-433, 1933.



Fig. 1.—*A*, nodular nonulcerating lesion on the dorsum of the right hand of a 77 year old housewife after an abrasion previously at this site. She received roentgen therapy (1,000 r \times 4). One year later the area previously treated by roentgen radiation was excised, but pathologic examination showed no evidence of malignancy. At the time of writing she is 81 years of age with no evidence of recurrence. *B*, photomicrograph of lesion before treatment.

Scars play a prominent part; in 19 of Mason's collected cases carcinoma developed in scars of old burns, and in 21, in scars from other injuries. Such trauma is probably a more important cause of carcinoma on the upper extremity than of carcinoma on other parts of the body, which are less subject to injuries.

Roentgen and radium irradiation have long played an important role in the production of carcinoma of the upper extremity, but from reports in the literature on this subject,⁴ lesions caused by these procedures are becoming less frequent, a result probably of more careful technic in the use of roentgen and radium radiation and the less enthusiastic use of roentgen radiation in treating certain skin diseases. It has taken physicians approximately thirty years to heed the warning of Ouidin, who in 1897 first observed that dermatitis and epithelioma frequently followed roentgen irradiation of skin.^{4b}

It has been estimated that lupus vulgaris accounts for cutaneous carcinoma in between 5 and 10 per cent of cases, and Mündelein⁵ reported that in 3.2 per cent of all instances of lupus vulgaris this lesion undergoes malignant degeneration. The University of Michigan series contains 1 such case (fig. 2).

The patient first had a lesion of his left forearm at 6 years of age. Alternately healing and ulcerating, the lesion remained troublesome until the patient was 44 years old; at this time it remained healed for fourteen years. When 70 years old, he was admitted to the University Hospital because the lesion had been ulcerated for two years, and at this time carcinomatous degeneration was noted. Amputation was done through the upper arm, followed by prophylactic roentgen irradiation of the axilla. Microscopic examination of the epitrochlear nodes revealed no abnormalities. He died at 75 of a cerebral hemorrhage, with no evidence of recurrence.

An analysis of the 36 cases studied at the University Hospital reveals that 32 patients were men and 4 were women; a ratio of 8 to 1. Sixty-four per cent had lesions on the dorsum of the hand; 19.4 per cent, on fingers or thumbs; 8.3 per cent, on the wrist, and the same per cent, on the forearm. The average time since the patients were first seen at the hospital was twenty-nine and a half months. At the initial examination, 44.4 per cent of all the patients had palpable epitrochlear or axillary nodes or both, and 50 per cent of these suffered recurrence or ultimately died of the carcinoma.

In table 2 no figure is given for the University of Michigan series under "Per Cent Cured" because the criteria used by other authors in determining which patients should be listed as cured are not clear.

4. (a) Handley, W. S.: The Treatment of X-Ray Carcinoma on X-Ray Dermatitis, *Lancet* 1:120-122, 1934. (b) Mason, M. L.: Carcinoma of the Hands and Feet, *Surgery* 5:27-46, 1939.

5. Mündelein, W., quoted by Mason.^{4b}

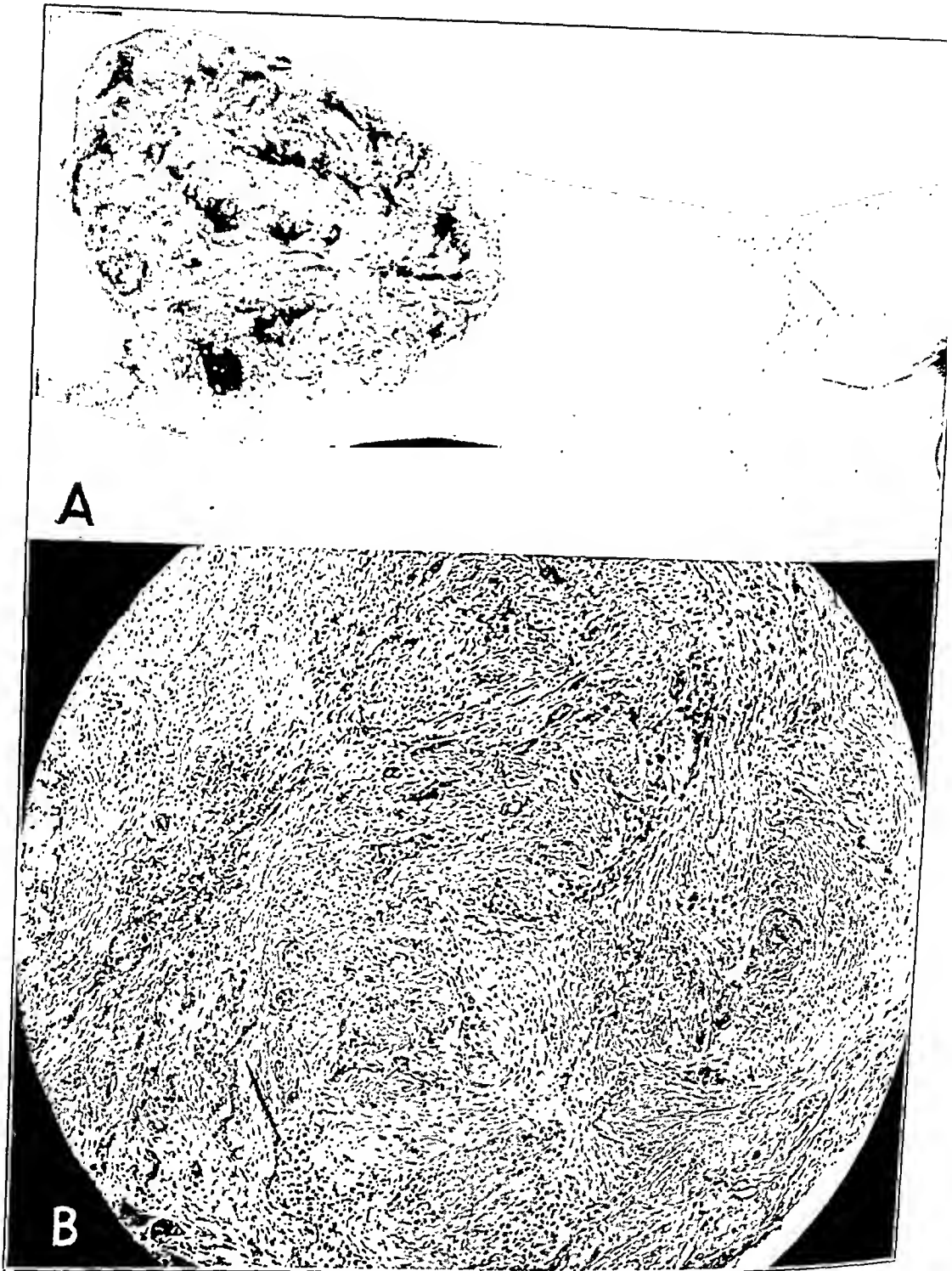


Fig. 2.—*A*, carcinomatous degeneration of lupus vulgaris mentioned in the text. The lesion was so far advanced that amputation through the upper part of the arm was done. The patient died five years later of a cerebral hemorrhage. *B*, photomicrograph of lesion.

TABLE 2.—*Comparison of Significant Features of Studies by Various Authors of Carcinoma of the Hand and Arm*

	Patients	Average Age	Ratio, Men to Women	Per Cent with Lesion on Dorsum	Per Cent with Metastases	Per Cent Cured	Ratio, Right to Left	Duration of Disease
Mason ¹ (collected cases)...	239	59	2 to 1	2-1	"Long course"
von Druan ⁶	97	35		
Mason ¹	25	50	2 to 1	94	51	65	1.0-1	2 to 3 years
Porter	43.5		
Schreiner, B. F., and Wehr, W. H.: <i>Am. J. Roentgenol.</i> 32:536-533, 1934	101	81	50	48		
DeBell, P. J., and Stevenson, T. D.: <i>Surg., Gynec. & Obst.</i> 63:222-259, 1936	51	58.3	3.5 to 1	70	37	72	...	1½ years
Broders ²	4 to 1					
DeWals ²	2.5 to 1					
Univ. of Michigan Hosp....	36	61.6	8 to 1	63.8	41.4	..	1.1-1	29½ months

If five year periods of survivals are used to reach this figure, then only 11 per cent of the patients of this series have been cured, for only 4 patients have lived five years or more without recurrence. Many patients in the University of Michigan series, however, died of intercurrent disease, without evidence of recurrence, before the five year period was reached. If these can be included, 33 per cent of this series can be considered cured. Further, if all patients who have neither died nor suffered recurrence but who have not as yet reached the five year period of survival can be included, the per cent cured jumps to 72. This, ultimately, may become the true "per cent cured."

One interesting phase of this study is the incidence of coexistent malignant neoplasms in other parts of the body. Von Brunn⁶ in 1903 noted 8 cases in which carcinoma of the extremity occurred separate from malignant neoplasm of some other structure. Other authors have either failed to record such an observation or considered it unimportant. In this series of 36 cases there were 18, or 50 per cent, in which other, proved unrelated neoplasms were present. All these were diagnosed as carcinoma of the skin (several were of the basal cell variety); 14 occurred on the face and 4 on other extremities.

In respect to the pathologic classification, 34 were squamous in type; 1 was mediocellular, and 1 was an adenocarcinoma of sweat gland origin.

The efficacy of treatment of these lesions has been subject to some debate, but operation and roentgen or radium irradiation of the site still remain the most popular procedures in the treatment of the local lesions as well as of the involved lymph nodes. Curet and cautery are occasionally employed for small local lesions. In the cases in which some type of surgical procedure was used for a local lesion, local excision, with and without graft, and amputation were the methods employed, as follows: local excision without graft, 3; local excision with graft, 10; amputation of finger, 4; amputation of arm, 2. Of these, recurrence has occurred in 1 case of local excision without the use of a graft.

Eleven patients were given active treatment to the lymph nodes. Six had roentgen radiation in fractionated doses; 1 of these ultimately died of his carcinoma. The remaining patients had no evidence of recurrence. Four had axillary and epitrochlear gland resection; 1 of these also died of his carcinoma. There was no evidence of recurrence in the remainder. One patient had both resection of axillary lymph nodes and roentgen radiation in fractionated doses to the axilla and ultimately succumbed to the effects of the carcinoma.

6. von Brunn, M.: Ueber den primären Krebs der Extremitäten, Beitr. z. klin. Chir. **37**:227, 1903.



Fig. 3.—*A*, lesion on the dorsum of the left hand of an 81 year old farmer. The lesion when examined at the University Hospital was several years old. Four years prior to this examination he had received six roentgen treatments, which failed to cause regression in the size of the lesion. Excision by the local physician a year later appeared to be successful when the lesion remained healed for one year. Caustic irradiation (5,000 r \times 2) at the University Hospital, and one month later local excision, left a defect which showed no evidence of healing. Accordingly, an amputation through the upper one third of the left forearm was done. The patient died of a coronary occlusion on the fourth postoperative day. *B*, photomicrograph of lesion.

Caustic or fractionated doses of roentgen radiation (and in 1 case radium) were used in treating the local lesion in 8 cases; in 4 of these there later was local recurrence.

Severe or widespread metastases were present at examination or developed subsequent to treatment in 9 patients, only 1 of whom was alive at the time of writing. This patient had surgical excision of the local lesion with fractionated doses of roentgen radiation to the axilla, and subsequently metastasis in an axillary node was discovered. The other 8 had metastases as follows: 2, axillary metastases; 1, cervical and pulmonary metastases; 1, axillary and pulmonary metastases; 2, widespread metastases revealed by necropsy; 1, widespread metastases, observed clinically; 1, a metastasis from another primary neoplasm. Of these patients, only 3 were actively treated: 1 had roentgen radiation to the axilla here after axillary dissection elsewhere; 1 had amputation of a finger with roentgen radiation to the axilla; 1 had amputation of an arm with axillary dissection and roentgen radiation to the axilla. The remaining patients had only biopsy for diagnostic purposes.

Although 15 patients of the 36 died, only 7 died of causes attributed directly to carcinoma. Eight died from intercurrent disease. It is interesting to observe that the average age of those dying from cancer was 52.7 years, whereas the average age of those dying from intercurrent disease was 75 years. Of the group dying from cancer, the 3 who had significant treatment lived thirty-four and six tenths months after treatment while those who had disease too far advanced to warrant active treatment lived twenty months after examination here. The average time of death after the institution of treatment in those patients dying from other causes was eighteen and six tenths months.

SUMMARY

Carcinoma of the hand or arm, although not frequent, is too often overlooked or undertreated. Vigorous early treatment must be carried out if good outcome is to be expected. In the experience of the University Hospital, wide surgical excision of the local lesion and a combination of surgical procedure and roentgen irradiation of the regional nodes have yielded the best results.

An analysis of 36 cases is presented.

INTESTINAL OBSTRUCTION

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I. POSSIBLE ROLE OF BACTERIA IN INTESTINAL OBSTRUCTION

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When one appreciates the breadth of physiologic applicability of the problem of intestinal obstruction, one can understand why the disorder has occasioned such an extravagant number of theories, prolific writings and extensive investigations. Unfortunately, too many glamorous sophisms have been dogmatically attached to attempted solutions of the problems presented by the group of disorders listed under the heading of intestinal obstruction.

Too often the physician conceives of the problem of obstruction as applying only to an acute mechanical blockage of the lumen of the intestine. It seems safe to assume that paralytic ileus from many causes not connected with direct mechanical obstruction of the lumen of the intestine may frequently, in the end, cause death by exactly the same processes as direct blockage of the lumen. Perhaps this applies in at least some instances to death from ileus secondary to peritonitis—death that would not occur were it not for ileus. It therefore does seem that when the unknown aspects of intestinal obstruction are solved, physicians will be able to apply this new knowledge more widely than to acute mechanical obstruction alone.

Though several excellent reviews on this subject have appeared within the past few years, it nevertheless seems desirable that we recapitulate the literature to a certain extent, in order to establish more clearly the premises on which we initiated the experimental work which we report in this paper.

This recapitulation and a discussion of the progress, or lack of it, which has been made toward establishing the true cause or causes of death in intestinal obstruction since the demonstration by Hartwell and

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Houget of the importance of the loss of fluids and essential salts may well be opened by quoting from the well known article of Murphy and Vincent¹:

There are three principal theories of the cause of death in acute intestinal obstruction, based on the observations of many clinicians and laboratory workers.

1. The theory of infection; that is, by the direct passage of organisms through the wall of the obstructed intestine into the peritoneal cavity, a fatal peritonitis is caused.

2. The theory of nervous reflex, which attributes the collapse and lethal result to the irritation of the nerve filaments of the intestinal wall.

3. The theory of auto-intoxication, which attributes the clinical symptoms to the absorption of some substance produced in the contents of the obstructed intestine. Attempts to determine the source of this toxic substance have divided the adherents of the theory of auto-intoxication into two groups. One group of investigators holds that the substance is due to the activity of the micro-organisms, which multiply within the obstructed intestine; the other believes that the essential factor is some disturbance in the secretion of the intestine itself.

For the sake of completeness the following theories may be mentioned in addition to those listed above:

4. Loss of blood and plasma into involved loops.

5. Destruction of tissue protein (loss of protein, excess of nonprotein nitrogen and urea in the blood).

6. Hyperpotassemia.

7. Adrenal cortex insufficiency.

8. Failure of the contents of the upper part of the bowel to mix with the contents of the lower part.

The hyperpotassemia theory² (and the occurrence of hyperpotassemia as a morbid factor in the human being has been questioned) is not itself a complete hypothesis, since the hyperpotassemia when it occurs is secondary to alterations in the adrenal glands or other organs, the latter alterations being due to the primary toxic factors in obstruction.

There are many arguments against the theory that death occurs because the contents of the upper part of the intestine do not mix with the contents of the lower in obstruction. Whipple³ made a specific experiment in this regard. He produced a closed loop in the duodenum just below the ampulla of Vater. He then established anastomosis between the stomach and the intestine below the obstruction permitting

1. Murphy, F. T., and Vincent, B.: *An Experimental Study of the Cause of Death in Acute Intestinal Obstruction*, Boston M. & S. J. **18**:684, 1911.

2. Scudder, J.; Zwemer, R. L., and Whipple, A. O.: *Acute Intestinal Obstruction*, Ann. Surg. **107**:161 (Feb.) 1938.

3. Whipple, cited by Hewlett, A. W.: *Pathologic Physiology*, New York. D. Appleton and Company, 1916.

food, as well as bile, pancreatic juice and gastric secretion, to pass freely into the unobstructed part of the intestine. The dogs thus treated died in from thirty-six to seventy-two hours.

In speaking of adrenal cortex insufficiency Wohl and co-workers⁴ said: "Indeed, we described the histologic changes of the adrenal gland in the dog with high intestinal obstruction as that of lipid exhaustion of extreme degeneration of the adrenal cortex." They stated that Kendal had separated two fractions from extract of adrenal cortex, one which produced results when salt was administered with it. They emphasized the many features in common between acute intestinal obstruction and adrenal cortex insufficiency and also emphasized the apparent benefit from combined administration of physiologic solution of sodium chloride and adrenal cortex extract in combating the toxemia from high intestinal obstruction. Certainly, however, degeneration of the adrenal cortex when it occurs, like hepatic degeneration,⁵ is an end result of more fundamental and primary alterations, which undoubtedly can cause death in the absence of either hepatic or adrenal cortex degeneration.

It is now generally accepted that the patient with high obstruction may die from a loss of fluid and salts if substitution therapy is not instituted even though strangulation or marked distention does not occur. Exclusive of this cause of death (loss of fluids and salts), the nerve reflex theory (next to the autointoxication theory) is probably the most popular at present.

A discussion of the nerve reflex theory was recently presented by Antoncic and Lawson.⁶ They cited the work of Herrin and Meek,⁷ who placed in the intestines of dogs balloons having pressures of 50 to 80 mm. of mercury. Herrin and Meek disposed of the toxin as the cause of death when they found that despite free drainage of Thiry-Vella nondenervated loops death occurred in the animals, whereas when they denervated draining loops they prolonged the lives of some of their animals.

Antoncic and Lawson in support of their arguments also mentioned that Ender and Herrin⁸ divided the jejunum 25 cm. from the ligament

4. Wohl, M. G.; Burns, J. C., and Pfeiffer, G.: High Intestinal Obstruction in the Dog Treated with Adrenal Cortex, *Proc. Soc. Exper. Biol. & Med.* **36**:549 (May) 1937.

5. Boyce, F. F., and McFetridge, E. M.: Acute Intestinal Obstruction, *South. Surgeon* **6**:109 (April) 1937.

6. Antoncic, R. F., and Lawson, H.: The Neurogenic Factor in Intestinal Obstruction, *Surg., Gynec. & Obst.* **72**:728 (April) 1941.

7. Herrin, R. C., and Meek, W. J.: Distention as a Factor in Acute Intestinal Obstruction, *Arch. Int. Med.* **51**:152 (Jan.) 1933.

8. Ender, E. C., and Herrin, R. C.: The Relative Importance of Toxemia in Jejunal Obstruction in Dogs, *Am. J. Physiol.* **126**:P485 (July) 1939.

of Treitz, inverted both ends of the sectioned bowel by means of a purse string suture and anastomosed the caudad end to the stomach or to the lower portion of the duodenum. The fluid from the obstructed bowel was returned to the normal bowel so that there was only slight loss from vomiting. Four dogs thus treated lived eight days, two weeks, four weeks and six weeks, respectively. The death on the eighth day was preceded by perforation of the bowel. These investigators (Ender and Herrin) then denervated the loops of 2 animals which had been operated on as described. One of these animals remained without symptoms for sixteen days and then died within a few hours after the onset of symptoms. The other dog with a denervated loop was reported normal on the eighteenth day of obstruction. Since the dogs survived "far beyond the eight days," excepting the one with perforation, they concluded that toxemia is of less importance in acute obstruction than chemical or nervous factors.

Taylor and associates⁹ prolonged for hours the lives of dogs whose intestines were distended with balloons by placing next to the balloons, in the intestinal lumens, a by-pass of heavy-walled rubber tubing and concluded that efferent nerve impulses are an important factor in death.

Other investigators—for instance, Fine and co-workers¹⁰—concluded that resection of splanchnic nerves and exclusion of the afferent nerve supply from obstructed loops do not influence the survival time of animals with intestinal obstruction.

Antonczic and Lawson⁶ themselves produced obstruction of the jejunum 15 cm. from the ligament of Treitz by resecting a 10 to 12 cm. segment and inverting the ends to form a closed loop. They reestablished the continuity of the gastrointestinal tract by an end to end anastomosis. Of 10 nondenervated control animals thus treated, all died in thirty-six hours to seven days, the average period being approximately seventy-two hours. At autopsy 7 dogs had perforation, and 3 dogs distention, of the loops. Of 23 dogs in which the nerve supply of the isolated loop had been destroyed, 12 died in three to four days, and 11 lived longer. At autopsy of the 12 animals which died, the loop of 1 dog was found perforated, and death was attributed by Antonczic and Lawson to peritonitis. Five of the 11 which lived longer than three to four days were killed in from four to eight weeks and while they were considered normal. These animals did not vomit after the first day or two, ate well and were active and alert. Postmortem examination showed that 3 of the 5 killed dogs had collapsed loops containing 10 to 20 cm. of gray mucous fluid, while

9. Taylor, N. B.; Weld, C. B., and Harrison, K.: *Experimental Intestinal Obstruction*, *Canad. M. A. J.* **29**:227 (Sept.) 1933.

10. Fine, J.; Rosenfeld, L., and Gendel, S.: *The Role of the Nervous System in Acute Intestinal Obstruction*, *Ann. Surg.* **110**:111 (Sept.) 1939.

2 had "markedly distended" loops. A culture from one of the latter yielded a pure growth of hemolytic and nonhemolytic streptococci. The remaining 6 animals of the group of 11 died in from three to four months and were considered entirely normal until one to three days before death, when they became listless, vomited and refused to eat. The authors made the following comment:

Four dogs dead of internal herniation and volvulus apparently had acute accidents avoidable with better surgical technique. Why two animals should suddenly develop a generalized acute gangrene after 3 and 4 months of normal livelihood is not apparent.

In the face of the work just reviewed and the comments relative to the part of nerve reflexes in the morbid picture it is interesting to quote again from the article of Murphy and Vincent of 1913:

While the nerve reflex theory might explain the symptom-complex, no positive evidence supporting this theory has been produced. Moreover, section of the splanchnics which wholly disconnects the intestine from the central nervous system fails to alter in the least the fatal course of the infection. Therefore, in our opinion, the nerve reflex theory, which may account for some of the early symptoms, fails to furnish a basis for a satisfactory explanation of the fatal course.

We believe that the foregoing statement of Murphy and Vincent still holds today. Certainly, though the work of Antoncic and Lawson is a worth while contribution to the literature, it and the previous work cited by these men as contributing to proof of the neurogenic factor in death cannot be taken as conclusive. Of the 5 dogs in the series of Antoncic and Lawson killed in four to eight weeks, animals which were considered normal at the time they were killed, 3 were found to have collapsed loops. In 2 of the animals the isolated loops were considered "markedly distended," but "markedly distended" is an insufficient description on which to base the conclusion that the dogs' lives had been prolonged by denervation of the loops. And as to the 6 animals with denervated loops which lived for three weeks to four months, surely the degree of distention of the loops during the interim was unknown. Undoubtedly, severe and consistent distention was not present or perforation of the loops would have ensued from interference with the blood supply. And it is unusual that 4 of the 6 dogs died of "internal herniation and volvulus," an "acute accident avoidable with better surgical technique." The remaining 2 of these 6 dogs died of gas bacillus infection.

Albeck¹¹ was one of the few investigators who worked with strangulated loops previous to 1913. He strangulated loops of ileum from 15 to 20 cm. long and advocated the autointoxication theory

11. Albeck, V.: Arch. f. klin. Chir. 65:569, 1902.

previous to Murphy and Vincent. Albeck, as quoted by Murphy and Vincent, concluded that:

1. The material obtained from these obstructed [strangulated] loops, when injected into other animals, reproduces these typical symptoms [of obstruction].
2. This material, after being passed through a Chamberland filter, is still toxic for the injected animal.
3. The extract of the intestinal content, even after boiling, is toxic.

Albeck believed the toxic substance was due to the putrefactive poisons.

As cited by Murphy and Vincent, the observations of McClure¹² are interesting because he showed that when bile and pancreatic juices were diverted from the obstructed intestine toxemia developed nevertheless; in other words, the toxin of obstruction, according to McClure, was formed independently of the pancreatic and biliary secretions.

Murphy and Vincent concluded that Kukula, Albeck, Borszaky and Genersich, Clairmont and Ranzi, McClure, Braun and Boruttau had published the most exhaustive and suggestive articles in support of the bacterial origin of toxic agents in intestinal obstruction up to the time of their report in 1913. But they emphasized that practically all previous workers with the exception of Albeck had worked with obstructions other than strangulation. Murphy and Vincent considered the various methods of approach to the solution of the autointoxication problem and the lack of agreement of workers as inconclusive. They therefore themselves ligated in cats either the venous or the arterial blood supply or both to closed unwashed loops of small bowel at various levels (in each instance sufficiently extensively to produce gangrene in the closed loop). They then demonstrated that material from the *unobstructed* small bowel was relatively nontoxic when injected intraperitoneally into other animals. All the animals with ligation of the blood supply to an obstructed bowel died within approximately twelve to twenty-four hours, and the material from the loops when injected intraperitoneally into other animals proved to be very toxic.

They then studied the effect of heat and filtration on the material obtained from the involved loops.

They concluded that strangulation of the blood supply to an involved loop was the vital factor in the production of toxin in obstruction and that the toxin was produced within four to six hours after interference with the blood supply. They demonstrated that the toxic substances produced were destroyed by boiling, were not soluble in water and would not pass through a Berkefeld filter.

12. McClure, R. D.: An Experimental Study of Intestinal Obstruction, J. A. M. A. 49:1003 (Sept. 21) 1907.

Knight and Slome¹³ recently contributed an instructive study, which has been rather widely cited and commented on editorially. They worked with the closed loop of small intestine, the latter being strangulated at about the midportion. The loop was unwashed in every case except the one to be mentioned. They demonstrated a marked depressor toxin in the loop of strangulated intestine, which appeared within thirty minutes after strangulation, and concluded that because of the rapidity of appearance the toxin could not be bacterial in origin. They admitted, however, that bacterial invasion of devitalized tissue and subsequent proteolytic action might later produce further toxic substances from the tissues of the intestinal wall other than their depressor substance. They stated that they were not yet in position to identify the substance or substances concerned with the depressor reaction but cited the work of Euler and Gaddam¹⁴ as demonstrating that muscle of intestine is the source of a depressor substance which evokes a blood pressure reaction very similar to those which have already been described. They also mentioned the work of Lim, Ling and Liu,¹⁵ who prepared an extract from intestinal mucosa and demonstrated effects which were even more comparable to those of their depressor substance. Lim and co-workers expressed the belief that this extract was a small mixture of histamine with the Euler-Gaddam-Fliex-Lange substance and that its effect was not due to acetylcholine, adenylyl compounds, kallikrein or Major's non-guanidine depressor substance.

Knight and Slome stated that their depressor substance was different from the toxic protease described by Whipple and co-workers,¹⁶ since it was dialyzable. Whipple and co-workers had concluded that impaired mucous membrane produced the lethal factor and that nothing produced in the lumen of the intestinal tract was concerned in the cause of death.

Knight and Slome, in order to determine whether the depressor substance was produced in the tissues of the intestinal wall or was a substance already present in the intestinal lumen which was absorbed following strangulation, divided the intestine transversely distal to the pylorus as well as above the ileocecal ends which had been severed and inserted a cannula into each end of the isolated segment of intestine.

13. Knight, G. C., and Slome, D.: Intestinal Strangulation, *Brit. J. Surg.* **23**:820 (April) 1936.

14. Euler, U. S., and Gaddam, J. H.: An Unidentified Depressor Substance in Certain Tissue Extracts, *J. Physiol.* **72**:74 (June) 1931.

15. Lim, R. K. S.; Ling, S. M., and Liu, A. C.: Depressor Substances in Extracts of Intestinal Mucosa, *Chinese J. Physiol.* **8**:219 (Aug. 15) 1934.

16. Whipple, G. H.; Rodenbaugh, F. H., and Kilgore, A. A.: Intestinal Obstruction Versus Protease Intoxication, *J. Exper. Med.* **23**:123 (Jan.) 1916. Whipple, G. H.; Stone, H. B., and Bernheim, B. M.: Intestinal Obstruction, *ibid.* **17**:286 (March) 1913.

They then washed out the intestinal lumen with 4 to 5 liters of warm water until the washings were clear. The water was then displaced with air and about 80 to 100 cc. of warm saline solution introduced. After half an hour the saline solution was displaced and an equal volume of fresh saline solution introduced. The intestine was then strangulated by ligating the superior mesenteric vein for a period of one hour. At the end of this time the saline solution was again displaced from the lumen and a sample of blood removed from a mesenteric vein. Two samples of saline solution from the lumen were thus obtained, the first from nonstrangulated intestine and the second from strangulated intestine. Each sample was filtered and the filtrate centrifuged. The first sample appeared clean and the second slightly blood stained. These samples were then tested by being injected intravenously into the normal animals, and in every case it was found that whereas saline solution from the nonstrangulated intestine was without effect, the washing from the intestinal lumen after the intestine had been strangulated for one hour was definitely depressor.

It has been known for many years that in many cases of obstruction (not all) there is considerable destruction of tissue protein with excessive amounts of nonprotein nitrogen and urea in the blood. Well informed clinicians as well as experimental investigators now recognize that in any disorder accompanied by loss of protein or low intake of protein replacement of the lost protein or supplementation of the ingested protein (by blood plasma, blood or prepared protein) is often as essential as the administration of the more commonly used fluids (dextrose and saline solutions). Several investigators have called attention to the deleterious loss of blood and plasma into obstructed loops and have expressed the belief that shock from such loss may cause death. Knight and Slome, however, reported a series of experiments from which they concluded that loss of fluid "plays at most only an accessory role in the production of circulatory collapse resulting from medium loop strangulation." After study of long loop strangulations they disagreed with Holt¹⁷ and stated that they did not consider even the hemorrhage or loss of fluid into these long loops as being responsible for death in intestinal obstruction and that certainly if death did result from such a cause it did so exceptionally. Our own opinion, based on the literature as well as on experimental work on venous mesenteric occlusions, leads us to agree with this statement of Knight and Slome. And though protein therapy in the form of administration of blood plasma is of great benefit when sudden or slow loss of plasma or of tissue protein has occurred, we know of no work which has proved it to be life saving in itself when absorption

17. Holt, R. L.: The Pathology of Acute Strangulation of the Intestine, *Brit. J. Surg.* **21**:582 (Oct.) 1934.

of products associated with markedly degenerating intestinal tissue is permitted to continue.

Kocher,¹⁸ as early as 1877, working with strangulated intestines in rabbits, concluded that peritonitis was not the cause of death in intestinal obstruction, and a sufficient number of subsequent workers have confirmed his opinion.

Nesbitt,¹⁸ studying the intestinal contents above occlusion of the small intestine in dogs which were fed food rich in lecithin, obtained choline and neurine and expressed the belief that these were lethal factors.

Gerard¹⁹ reported that he had demonstrated histamine as a toxin of intestinal obstruction.

Murphy and Brooks²⁰ isolated a closed intestinal loop and reestablished the continuity of the bowel. They found that when the closed intestinal loop was rendered sterile by long-continued drainage and then was closed it was compatible with life even though strangulated. Dragstedt and associates²¹ found that the closed intestinal loop was compatible with life if the bacteria in the loop had been eliminated by drainage before closure.

Haerem, Dack and Wilson²² and others have concluded from experiments that Williams²³ was incorrect in assuming that Welch bacilli have something to do with toxicity in intestinal obstruction. Williams advanced this hypothesis in 1926. He passed the intestinal fluid from the obstructed loops through a Berkefeld filter. He injected 0.75 cc. of the filtrate with 0.25 cc. of normal horse serum into mice intramuscularly; into another group he injected 0.75 cc. of filtrate together with 0.25 cc. of Welch antitoxin. He tabulated striking results showing large numbers of deaths in the first group and none in the second. The mice were observed for six days.

18. Cited by Ellis, J. W.: The Cause of Death in High Intestinal Obstruction, *Ann. Surg.* **75**:429 (April) 1922.

19. Gerard, R. W.: Chemical Studies on Intestinal Obstruction, *J. Biol. Chem.* **52**:111 (May) 1922.

20. Murphy, F. T., and Brooks, B.: Intestinal Obstruction: An Experimental Study of the Causes of Symptoms and Death, *Arch. Int. Med.* **15**:392 (March) 1915.

21. Dragstedt, L. R.; Moorhead, J. J., and Burcky, F. W.: Intestinal Obstruction in Closed Intestinal Loops, *J. Exper. Med.* **25**:421 (March) 1917. Dragstedt, L. R.; Dragstedt, C. A.; McClintock, J. T., and Chase, C. S.: Intestinal Obstruction, *ibid.* **30**:105 (Aug.) 1919.

22. Haerem, S.; Dack, G. M., and Wilson, H.: Acute Intestinal Obstruction: Role of Bacteria in Closed Jejunal Loops, *Surgery* **3**:333 (March) 1938.

23. Williams, B. W.: Importance of Toxemia Due to Anaerobic Organisms in Intestinal Obstruction and Peritonitis, *Brit. J. Surg.* **14**:295 (Oct.) 1926.

Haerem, Dack and Wilson used a closed loop of the upper part of the jejunum; the length in the different animals varied from 15 to 30 cm. They sectioned the loop at each end and closed the ends by purse string sutures; then they reestablished the continuity of the bowel around the loop.

When the animals appeared to be critically ill, usually thirty-six to seventy-two hours after operation, a second laparotomy was done and the obstructed loop removed. The fluid from this excised loop was immediately placed in sterile containers and used for bacteriologic examination and toxicity studies.

The loop contents were centrifugalized at high speed for forty-five minutes and the supernatant fluid carefully removed and used for mouse inoculations. Mice weighing from 17 to 20 Gm. were given from 0.2 cc. to 0.5 cc. of fluid intravenously, control animals being given the same quantity together with 0.05 cc. of *Cl. welchii* antitoxin. Deaths of mice occurring within forty-eight hours only were recorded.

A strain of Welch bacilli, which in most instances was capable of producing a potent toxin in vitro, was isolated for each animal. The investigators did not heat or filter the loop fluid before it was injected, feeling that prolonged filtration or heating might destroy the Welch toxin. They concluded that the Welch toxin was not the specific toxin of death in acute intestinal obstruction.

Trusler and Reeves²⁴ and others have called attention to the great variability in toxicity of *Clostridium welchii*. They quoted Brown and agreed with him, stating:

Brown, in a comprehensive study of anaerobic bacteria, has shown the variability of sugar fermentation even within a single strain. He concludes that anaerobes are divided into groups according to their ability to ferment sugars, and according to their proteolytic powers, but that they cannot be rigidly divided as being either saccharolytic or proteolytic. We have found that *C. Welchii* regularly ferments dextrose, sucrose, maltose and lactose with acid and gas, and that its proteolytic powers are very limited.

The organisms occupying the livers and muscles of the dogs studied by Trusler, Reeves and Martin did not produce an exotoxin but were all large gram-positive bacilli. Their morphologic characteristics and gas production could easily have permitted confusion of them with pathogenic forms when actually they were not pathogenic.

EVALUATION OF THE PRESENT STATUS OF THE LITERATURE AS TO FUNDAMENTAL LETHAL FACTORS

The greatest mass of evidence available at present indicates that there are two fundamental "chief concerns" in any given case of acute intestinal obstruction: first, loss of fluids and electrolytes; second,

24. Trusler, H. M., and Reeves, J. R.: Significance of Anaerobic Organisms in Peritonitis Due to Liver Autolysis, *Arch. Surg.* 28:479 (March) 1934.

interference with the blood supply. And since, as far as we know, the problem of replacement therapy (fluids and electrolytes, proteins in the form of blood plasma, blood and prepared proteins) has been rather well solved with regard to acute obstructions, the most serious primary concern in any case is usually the interference with the blood supply. This interference may come by direct obstruction of the mesenteric vessels to an intestinal segment as in strangulating volvulus or in mesenteric thrombosis; or, according to Gatch, Wangenstein, Van Buren, Sperling and others who have done careful experimental work in this regard, it may be produced by bowel *distention*. Gatch and Culbertson²⁵ concluded from their study that "intraintestinal pressure as low as 20 mm. of mercury produces an almost complete anemia of the mucosa of the bowels"; again Gatch, Trusler and Lyons²⁶ concluded from an experimental study that relatively low intraintestinal pressure, namely, 20 to 40 cm. of water, allows for damage and the onset of lethal factors in an obstructed bowel.

Wangenstein has made a great contribution toward control of interference with blood supply from distention in simple obstructions. And the Miller-Abbott tube combined with suction may be used still more effectively to decompress greater lengths of intestine in some instances. But, as Wangenstein himself warned, decompression therapy has not solved the entire problem of the interference with blood supply. Obviously, a closed loop obstruction cannot consistently be decompressed by Wangenstein suction or the Miller-Abbott tube, and when gangrene of the intestine is present the decompression therapy can be used only as an adjunctive treatment, the most imperative problem being to rid the body of the gangrenous intestinal tissue.

It is true that no one has proved that neurogenic factors associated with distention, adrenal cortex alteration, splanchnic dilatation, loss of fluid into the involved loop, disturbances of blood plasma volume, destruction of tissue protein and hyperpotassemia are not from time to time all complicating elements in the morbid picture. It is possible that some of these factors at times may assume an important role in the immediate final cause of death. But, as said, it seems that stress has been laid too frequently on these "secondary factors" to the neglect, especially, of the fulminating factors which arise from serious interference with blood supply.

Of course, if some specific end result of interference with blood supply, such as hyperpotassemia or adrenal cortex insufficiency, could

25. Gatch, W. D., and Culbertson, C. G.: Circulatory Disturbances Caused by Intestinal Obstruction, *Ann. Surg.* **102**:619 (Oct.) 1935.

26. Gatch, W. D.; Trusler, H. M., and Lyons, R. E.: Toxemia in Acute Intestinal Obstruction, *Arch. Surg.* **28**:1102 (June) 1934.

be demonstrated as the specific cause of death secondary to the interference with blood supply, and some specific therapy could be rendered to counteract this immediate cause of death, then indeed would a step forward have been made. But no specific medical therapy has as yet been demonstrated as effectively slowing the tremendously rapid physiologic collapse which follows immediately on devitalization of intestinal tissue. But one must accept that as long as investigators are unable to prove more emphatically the exact nature of the toxins produced—for various investigators have repeatedly produced toxins from the intestinal wall uncontaminated by substances normally found within the intestinal lumen—that until the chemical nature and the pharmacologic effects of these toxins in other animals are well known, there will continue to be considerable confusion and discussion of many theories. And such confusion will, of course, cause uncertainty in the minds of physicians relative to the treatment of obstruction.

In evaluating the present status of the research and the clinical aspects of the problem it may be said that the past three decades have been a period in which investigators have traveled in a widening circle. They have stored additional and valuable knowledge in their files, and much of it may later prove to be of more practical value than it is at present. But if they are to clarify fully the problem of obstruction they must answer still more accurately and repeatedly the old fundamental questions:

1. Is there a lethal toxin or toxins liberated by degenerating intestinal wall which will produce death despite all present methods of therapy unless absorption of such products is stopped early?

2. If such toxin or toxins are present, what role do bacteria play in their production? Are toxins of bacteria themselves the lethal factor? Or are the toxins formed by the bacteria acting on the devitalized intestinal tissue?

3. Are toxic products which are normally present within the intestine absorbed as the injured wall becomes more permeable and are they a lethal factor?

4. If toxic products of protein degeneration are present, what is their nature? Are they absorbed in sufficient quantity to cause death and what is the pharmacologic action of such toxins?

METHODS AND OBJECTIVES OF OUR EXPERIMENTAL PROCEDURES

We set about with the purpose of, so far as possible:

1. Obtaining as pure and uncontaminated products of degeneration as we could from the *wall* of the *small intestine* at an early hour after ligation of the blood supply to the loop selected.

2. Selecting sufficiently small animals for injection of the products of degeneration to permit us to have a larger series of experimental animals on which to study the pharmacologic effect of toxin than would be possible in proportion if the products were injected in larger quantities into fewer animals.

3. Establishing control studies to demonstrate the relative nontoxicity of secretions from the clean wall of the nonstrangulated intestine.

4. Determining whether bacteria are essential to the production of any toxin found.

5. Determining whether the toxin of the bacteria themselves could be a factor.

6. Studying the chemical nature of any toxin produced.

We do not claim to have decisively attained all the stated objectives, but the experiments have been done carefully, and we have every confidence that if other investigators proceed with the same meticulous effort along exactly the same lines of procedure, they will be able to confirm our conclusions so far as they go.

GROUP I

STUDY OF NONSTERILE NORMAL SECRETIONS

The objective in this group was to ascertain whether the normal ileac secretions of dogs were toxic to mice when injected intraperitoneally in quantities equal to lethal doses (by volume) of the secretions obtained after ligation of the blood supply.

Ten dogs were used in this group.

Some preliminary experiments not listed here were done as we established the standard dose of 8 minims (0.5 cc.) for the intraperitoneal injections, which was the dose generally used in this and subsequent groups.

Dog 7, series 8A, was operated on under ether anesthesia, with no preliminary medication, Feb. 9, 1939. At 11:20 a. m., a 15 inch (38 cm.) loop of the lower part of the ileum was isolated and thoroughly washed with tap water running through a tube until all gross matter had been removed and the return was perfectly clear. The loop was then stripped "dry." The blood vessels and lymphatics to the loop were *not* tied. All ends of loop and intestine were closed without any medicaments being instilled into the loop. The latter was then returned to the abdomen. At 1:24 p. m. of the same day (giving a two hour specimen) the abdomen was again opened, without anesthesia, and about 45 cc. of moderately clear thin fluid was obtained from the loop. The latter was then closed and returned to the abdomen.

Promptly 8 minims of this unfiltered, untreated, undiluted fluid was injected intraperitoneally into each of 4 mice. All the mice recovered and did not seem ill at any time.

The abdomen of the dog was opened again at 4:15 p. m., and 30 cc. of the same kind of fluid was taken from the then distended loop, and 8 minims injected intra-

peritoneally into each of 3 mice. These mice recovered. All the injections of both specimens were made promptly after the removal of the fluid from the loop.

Gram-stained smears, 1 cm. square, of the loop fluid were examined with results as follows: Specimen of 11:13 p. m. (from washed intestinal wall), 0 bacteria per oil immersion field; specimen of 1:45 p. m., 0 bacteria per oil immersion field; specimen of 4:15 p. m., 1.5 gram-positive rods (morphologically *Cl. welchii*) to the oil immersion field.

Four additional dogs were treated in exactly the same manner as described for dog 7, series 8A; smears of the relatively clear fluid obtained were examined, and each specimen from each dog was injected intraperitoneally into 5 mice. The specimens presented bacterial counts running from 0 to 10 micro-organisms per oil immersion field (the micro-organisms being morphologically almost exclusively *Cl. welchii*). All of the 20 mice recovered except 4 (2 received specimens from each of 2 dogs, the specimens containing 8 to 10 micro-organisms per field). These 4 mice died in thirty-six to forty-eight hours.

In 2 additional dogs there was insufficient fluid in the loops at two and four hours to permit intraperitoneal injections in mice.

In 3 other dogs the loop fluid in five hours showed 30 to 200 micro-organisms resembling *Cl. welchii* per oil immersion field. Material from the loops of the 3 dogs was injected into 25 mice and all except 1 mouse died within twenty-four hours. Autopsy of the mice left us undecided as to whether the animals died of peritonitis.

CONCLUSIONS FROM GROUP I

1. Thin, relatively clear, untreated, nonsterile, fresh, normal ileac secretions from dogs are not lethally toxic to mice when injected in relatively large doses (8 minims) intraperitoneally provided the bacterial content of the fluid is low (arbitrarily below 8 to 10 micro-organisms per oil immersion field).

2. Normal fresh ileac secretions mixed with flocculent products (probably protein in nature) from the ileum and showing a high bacterial count (micro-organisms having the morphologic characteristics of *Cl. welchii*) kill mice within twenty-four hours when injected intraperitoneally in 8 minim doses.

GROUP II

A CONTROL DETERMINATION OF THE TOXICITY OF NONSTERILE SECRETIONS FROM ILEAC LOOPS WITH STRANGULATED BLOOD SUPPLY

Having determined by the experiments of group I that the normal nonsterile secretions were not lethal or apparently toxic to mice on intraperitoneal injection in 8 minim doses if the bacterial counts on smears from the secretions were low (arbitrarily 8 to 10 micro-organisms per oil immersion field or less), we next injected into mice 8 minim doses of nonsterile secretions from lower ileac loops to which all of the blood supply had been ligated.

Eight dogs were used in this group. The technic of the production and collection of fluid, as illustrated in the following protocol, was the same for each experiment.

Dog 8, series 8A, was operated on March 18, 1939 at 9:05 a. m., under ether anesthesia, with no preliminary medication. About 15 inches of the lower part of the ileum was isolated, the open ends of the bowel from which the loop had been detached were promptly closed, all arteries and vessels to the loop were ligated, and the loop was washed thoroughly by running tap water until the return was completely clear; the loop was then stripped dry and returned to the abdomen. At 12:30 p. m. (giving a three hour forty-five minute specimen) 22 cc. of bloody fluid was collected; the loop was closed and returned to the abdomen.

Gram-stained smears, 1 cm. square, of this specimen showed 12 bacilli (morphologically *Cl. welchii*) per oil field. No other bacteria were seen.

Intraperitoneal injections were made in thirty-one mice. The results may be summarized without taking space to report the experiments in greater detail. We had previously demonstrated that the intraperitoneal injection of 1 cc. of fresh polyvalent *Bacillus perfringens* antitoxin (Lilly) does not kill full grown mice.

SUMMARY OF STUDIES OF GROUP II

Eight minim doses of the nonsterile fluid obtained from cleansed loops of ileum three hours and forty-five minutes after the ligation of the blood supply to the loops and injected intraperitoneally into mice killed all the mice.

The only micro-organisms found on Gram-stained smears were gram-positive and were morphologically *Cl. welchii*. The only additional identification procedure used was the usual milk culture, which also indicated *Cl. welchii*.

Intraperitoneal and subcutaneous injections of fresh polyvalent *B. perfringens* antitoxin in 1 cc. doses did not protect mice from these nonsterile products procured from ileac loops after the blood supply to the loops had been ligated for three hours and forty-five minutes. No demonstrable protection was obtained when the fresh toxic loop fluid was mixed with an equal amount of the fresh polyvalent antitoxin and the mixture allowed to stand in a test tube for a period of forty-four minutes before being injected intraperitoneally.

It could be legitimately argued that peritonitis alone killed these mice. The manufacturers of the *B. perfringens* antitoxin do not claim that the product destroys bacteria. However, autopsies of the mice left us uncertain that any of the animals died of peritonitis. Furthermore, the majority of the mice survived intraperitoneal injections of 8 minim doses of nonstrangulated loop fluid containing only 12 of the micro-organisms with which we were working, per oil immersion smear. Therefore, though the studies of this group are not conclusive in themselves, we report them even though they were preliminary to the investigations, the reports of which follow.

GROUP III

THE TOXICITY OF FRESH MATERIAL FROM ILEAC LOOPS THE BLOOD SUPPLY OF WHICH HAD BEEN STRANGULATED (MATERIAL MADE STERILE BY BERKEFELD FILTRATION PREVIOUS TO INJECTION INTO MICE)

Having by the previous two groups of experiments partly reached a control basis from which to carry on the future experiments herein listed, having established that the normal secretion from ileac loops is in itself not lethal to mice in intraperitoneal 8 minim doses and having established that intraperitoneal 8 minim doses of nonsterile ileac secretion collected from the loops between three and four hours after the blood supply to the loops had been ligated were lethal, we set about to determine as best we could whether bacteria were necessary for the production of toxins in a strangulated loop and to determine whether bacteria were necessarily a cause of death by peritonitis in mice given intraperitoneal injections of the fluid.

Preparation of Filtrates.—In all the experiments in this group Berkefeld filtration was started immediately after the material had been collected.

Previous investigations not listed in this paper made it obvious that Berkefeld filtration presented some difficulties. We believed that the filtration should be completed as soon as possible in order to decrease the likelihood of in vitro change of toxic elements.

We found it necessary to dilute the material from the intestine to get it through the Berkefeld filters with a reasonable degree of rapidity. Distilled water was used for the dilution of some of the specimens and isotonic saline solution for the dilution of others. (No difference in toxicity was noted when ether diluent was used.) With five of the specimens a 1:1 dilution was satisfactory, with four a 3:1 dilution and with one a 4:1 dilution. Using these dilutions and carrying on the filtrations at room temperature, we were able to procure each filtrate and inject it into mice at the end of the same day that the original material was obtained from the loop.

Experiments.—Ten dogs were used in this group, the technic for each being the same.

Each was anesthetized with ether; no preliminary medication was used.

The lower 20 to 25 inches (50.5 to 63.5 cm.) of the ileum, to within 3 inches (7.5 cm.) of the ileocecal junction, was identified. The loop was then opened at each end and thoroughly lavaged with running tap water until the return was perfectly clear. (Caution was used in lavaging the loops, as in all other groups, to avoid damage to the loops by excessive pressure of water.) The loop was then stripped dry and the blood supply to it completely ligated. The open bowel ends were closed by ligature, the loop returned to the abdomen and the abdominal wall closed.

The abdomen was reopened without anesthesia in three and one-half to four hours and the reddish, blood-tinged thin to moderately thick fluid collected in a sterile beaker.

Smears were made of pooled and of separate specimens and showed 12 to 20 gram-positive micro-organisms, morphologically *Cl. welchii*, per oil immersion field. No other micro-organisms were seen.

In one experiment the entire material from the loops of 5 dogs was pooled, diluted 1:1 with distilled water and Berkefeld filtration immediately started. The filtrate was procured in the evening of the same day that the dogs were operated on and was proved sterile by culture and smear. Twelve mice were given single 1 cc. doses of this filtrate (this being equivalent to 8 minims of the original loop fluid by volume), injected intraperitoneally. Eleven of the 12 mice died before 11 o'clock the next day. At autopsy no unusual findings were noted. Some hyperemia of intra-abdominal structures was present in numbers of the animals, but we do not believe any of the mice died from peritonitis. The organs were not sectioned for microscopic study. The mice presented the same lethargic appearance after the injections that had been seen in mice of group II. One mouse recovered.

The loop fluid which could pass through the filter only after 4:1 dilution yielded a filtrate which in an 8 minim dose (equivalent by volume to only 2 minims [0.1 cc.] of the original fluid) was not uniformly lethal to mice. The same was true of the 3:1 dilutions.

CONCLUSIONS FROM GROUP III

Relatively potent toxin is formed in three and one-half to four and one-half hours within a cleansed strangulated loop of ileum in a dog. This toxin is lethal to mice in 8 minim doses when injected intraperitoneally after being sterilized by Berkefeld filtration.

GROUP IV

AN ATTEMPT TO NEUTRALIZE THE TOXIC MATERIAL OBTAINED IN THE FILTRATE OF GROUP III BY MEANS OF B. PERFRINGENS ANTITOXIN

A 10 cc. quantity of the sterile toxic material (the filtrate) from the 1:1 dilutions described in group III was taken for injection into 10 mice. In each of the 10 mice, 8 minims of fresh *B. perfringens* antitoxin was injected intraperitoneally. Two hours later 1 cc. of the toxic material (filtrate) was injected intraperitoneally into each mouse. Nine of the 10 mice were found dead within twenty-four hours. All injections were made the same day the original fluid had been collected from the loops of the dogs.

Postmortem examination of the mice revealed no findings of note. Peritonitis did not seem to be the cause of death in any. The organs were not sectioned for microscopic study.

CONCLUSIONS FROM GROUP IV

Fresh polyvalent *B. perfringens* antitoxin did not protect mice against toxin produced in the washed strangulated ilea of dogs.

GROUP V

ATTENUATION OF BACTERIAL PROLIFERATION IN ILEA WITH STRANGULATED BLOOD SUPPLY AND TESTING OF MATERIAL FORMED IN ABSENCE OF BACTERIAL PROLIFERATION

No dogs were used in this group.

In dog 3, series 8A, on Dec. 2, 1938, at 10:45 a. m., all arteries and an occasional vein to the lower 30 inches (76 cm.) of the ileum, beginning just proximal to the

cecum, were ligated. Ether anesthesia was used without preliminary medication. The loop ends were opened and the lumen thoroughly washed with running tap water until the return was clear. The loop was then stripped dry, and about 50 cc. of tincture of merthiolate was introduced into the loop and left there for twenty minutes. Then the loop was washed thoroughly with tap water until the return was entirely clear. After the tincture of merthiolate had remained in the loop for twenty minutes, a small segment of intestine was taken and preserved for microscopic study. (The microscopic report was that the cells and general structure of this membrane did not appear to have been damaged.)

After the loop was thoroughly washed and stripped, its ends were tied off, it was returned to the abdomen and the abdominal wall was closed. At 2:22 p. m. (giving a three hour twenty-three minute specimen) 5 cc. of pinkish red fluid, resembling thin crab meat gumbo, was removed. (This material passed through a small gage needle without difficulty as intraperitoneal injections were made.) The loop was then closed and returned to the abdomen.

(a) Four mice were each given an intraperitoneal injection of 8 minims of this 2:22 p. m. specimen. All these mice recovered.

(b) At 6:21 p. m. on the same day (giving a seven hour fifty-six minute specimen) about 10 cc. of thick bloody material was collected from the loop without anesthesia or medication. Smears, cultures and injections into mice were made. Six mice were given 8 minims each of this specimen. Five of the mice were found dead the next morning. Autopsies were made, and no evidence of severe peritonitis was present at gross examination. Our records do not show what happened to the remaining mouse. (Since this specimen and that described in the following paragraph were heavily loaded with bacteria, these results were not included in the table.)

(c) The loop, after the foregoing specimen had been taken and after it had been stripped, was again returned to the abdomen. The animal was opened again at 9 p. m. of the same day and another specimen taken. Five mice were given 8 minims each of this specimen intraperitoneally. All of these mice were found dead the next morning.

Bacteriologic Slides.—On the 2:22 p. m. (three hour twenty-three minute) specimen the average count was 0.04 per oil immersion field; on the 6:20 p. m. (seven hour twenty-six minute) specimen the average count was 40.4 per oil immersion field. On the 9 p. m. specimen the micro-organisms were too numerous to count; the estimate was 350 per oil immersion field.

From Aug. 13 to 16, 1940, 8 additional dogs were operated on. The loops were thoroughly lavaged as described for previous dogs in this group, stripped dry and treated by instillation of tincture of merthiolate, about 1 cc. to each inch of the 20 to 25 inch loops, the antiseptic being left in the loops exactly twenty minutes. The loops were then thoroughly lavaged with tap water, stripped dry and returned to the abdomens. They were left four to four and one-half hours and then the loop fluid from each animal was collected separately in a sterile beaker. Gram-stained smears were immediately made from the separate specimens. Six of the specimens showed no bacteria in the Gram-stained smear, and one showed 11 gram-positive micro-organisms, morphologically *Cl. welchii*, per oil immersion field. The latter specimen was discarded.

The results of the intraperitoneal injections made with the material from the 9 dogs of this study are given in the table.

Before the tincture of merthiolate was used in the manner described in group V various antiseptics (aqueous solution of merthiolate [1:1,000], hexylresorcinol [1:1,000], aqueous solution of iodine and 5 per cent aqueous solution of gentian violet) were left in the loops for twenty minutes to five hours and fifty-five minutes after the loops had been washed, in the hope that the bacterial count would be held down. We believed these solutions would be less likely to damage the mucous membrane than tincture of merthiolate. If these antiseptics had prevented bacterial proliferation and at the same time a toxic product had been formed in the degenerating loops, we could possibly have assumed from these experiments alone that toxin was formed from the intestinal wall without the influence of bacterial proliferation. However, with the exception of the aqueous solution of gentian violet the solutions mentioned did not hold down the bacterial proliferation to our satisfaction,

Summary of Experiments in Group V

Dog	Time Loop Fluid Collected After Strangulation	Mice Given Intraperitoneal Injections	Amount, Minims	Mice Recovered and Active Next Morning	Mice That Died Within 24 Hr.
6B	4-4½ hours	5	8	3	2
7B	4-4½ hours	5	8	4	1
8B	4-4½ hours	5	8	4	1
9B	4-4½ hours	3	8	2	1
10B	Discarded				
11B	4-4½ hours	3	8	3	0
12B	4-4½ hours	3	8	3	0
5S8A	2½ hours	5	8	5	0
3S8A	3½ hours	4	8	4	0
Total.....		33	..	28	5

and consequently these experiments were of no positive value. It was found that 1 cc. of a 1:1,000 aqueous solution of merthiolate injected intraperitoneally does not kill mice, and if it could have been proved that this substance prevented bacterial proliferation, this agent especially would have been of great value in determining the extent of toxin formation in the absence of bacterial proliferation.

It is claimed that the merthiolate in the tincture or in the aqueous solution of merthiolate does not combine with, or in itself chemically alter, protein products. One might wonder whether the alcohol or the acetone which is in the tincture of merthiolate could damage or alter the mucous membrane to the extent that a toxin was not produced whereas it would have been otherwise, even though bacteria had *not* been acting on it. This problem we have not attempted to solve altogether in this series. It is noted in a foregoing paragraph that the pathologist reported that the mucous membrane did not appear on microscopic study to have been damaged by the tincture of merthiolate.

We would call attention again to the work of Trusler, Reeves and Martin, since micro-organisms morphologically *Cl. welchii* were found almost exclusively in the specimens in our entire study. We believe it highly probable that bacilli of a single specific pathogenic type were not the exclusive factor in the production of the toxins we have studied. It seems probable that proteolytic micro-organisms morphologically *Cl. welchii* but not necessarily belonging to the specifically recognized pathogenic Welch bacillus types were responsible for the production of toxins through their proteolytic action.

It is possible that toxic protein products can be produced without the proteolytic action of bacteria as tissue degeneration slowly occurs. However, except possibly in newborn infants (and in patients with the high type of obstruction mentioned subsequently) bacteria are always prolifically present in the obstructed intestine. And for practical purposes it seems safe to assume that the toxins in obstructed intestines which are produced most rapidly, frequently and abundantly are the result of the proteolytic action of bacteria on damaged intestinal wall structures. This, of course, does not assume that in high nonstrangulated obstructions in which vomiting and emptying of the intestine occur sufficiently to prevent distention of the latter (this type occurs in a distinct minority) death cannot occur from loss of fluid and electrolyte alone, or that in the absence of proteolytic bacteria the toxins produced by nonproteolytic micro-organisms themselves, as for example streptococci, cannot be absorbed.

CONCLUSIONS FROM GROUP V

Toxic material is formed much less rapidly in the washed strangulated lumens of the ilea of dogs when bacteria are absent than when bacteria are present.

II. THE CHEMICAL NATURE OF THE TOXINS OF INTESTINAL OBSTRUCTION

BY J. K. DONALDSON, M.D.; E. B. SIVE, M.D., AND NORMAN LEWIS, M.S.

In July 1931 material was obtained from the loops of three groups of dogs on three different occasions. Twelve dogs were used in the first group, 8 in the second and 4 in the third. In each animal, 20 to 30 inches (50.5 to 76 cm.) of the lower part of the ileum was isolated and the lumen thoroughly lavaged by running tap water until all gross material was removed from the loop and the flow came through perfectly clear. The loop was then stripped as dry as possible and all arteries, veins and lymphatics to the loop were ligated. The bowel

ends were then closed and the loop returned to the abdomen. Ether anesthesia without preliminary medication was used for the first operation on each dog.

Four and a half to five hours later the abdomen was opened without anesthesia or medication and the contents of the loop stripped into a sterile glass container. The dogs were operated on early in the morning and the material obtained was promptly taken by the chemist, and work as related in subsequent paragraphs was started immediately. Caution was taken in each instance to carry the work promptly through to the stage at which, it was felt, alteration of toxin *in vitro* might be prevented.

In the studies on the three different groups, the steps were essentially the same, and the end results were essentially the same. To avoid reiteration, only the steps and the conclusions reached in the study of the third group are recorded.

Smears on the pooled specimens showed 14 to 25 gram-positive micro-organisms per oil immersion field, which morphologically were *Cl. welchii*. No other micro-organisms were seen.

CHEMICAL STUDIES ON TOXINS FORMED IN THE PRESENCE OF BACTERIA

A 200 cc. quantity of fluid taken from the loops of the obstructed intestines of the 4 dogs was diluted to one and a half times the original volume with distilled water; it was then centrifuged and the supernatant fluid filtered through paper. The filtered supernatant fluid was labeled solution A.

Effect of Heat on Toxicity of Loop Fluid.—A 30 cc. quantity of solution A was strongly centrifuged and filtered through a Berkefeld filter. This filtrate, free from bacteria, as proved by culture, was divided into two 15 cc. portions, 1a and 1b.

Portion 1a was heated for fifteen minutes in a boiling water bath, the coagulum thrown down in the centrifuge, and the supernatant liquid removed and labeled 1c. The coagulum was extracted with hot water and the extract added to the supernatant fluid, 1c. Portion 1c with the added hot water extract, now called portion 1d, was adjusted to a volume of exactly 15 cc.

Portions 1b and 1d were then compared as to toxicity. They were injected intraperitoneally into seven pairs of mice, each mouse weighing 19 Gm. (plus or minus 2 Gm.). Portion 1b was injected into 7 mice in the following doses, respectively: 4, 8, 12, 16, 20, 24 and 28 minims (0.24, 0.48, 0.73, 0.97, 1.2, 1.4 and 1.7 cc.). All these mice died in less than twelve hours. Portion 1d was injected similarly into 5 mice, in 12, 16, 20, 24 and 28 minim portions, and all these mice recovered. The remainder of 1d was then evaporated to half-volume and injected into 2 mice in 16 and 24 minim portions, corresponding to 32 and 48 minims (1.9 and 2.9 cc.) of the original solution, and these mice died in less than twelve hours.

From these results it appears that (since only 4 minims of 1b were required to cause death and a dose equivalent to 32 minims of 1d was required to produce the same result) the loop fluid was originally about

eight times as toxic to mice as it was after it had been held at 100 C. for fifteen minutes.

It seems that the toxicity of original loop fluid is due to at least two different chemical species; one is water soluble and coagulated by heat (or possibly decomposed without coagulation); while the second is water soluble and not destroyed or coagulated by heat.

Toxic Fractions Precipitated by Alcohol.—A 180 cc. quantity of loop fluid, solution A, was diluted to one and a half times its original volume with distilled water. It was then centrifuged, filtered and poured into 5 volumes of 95 per cent alcohol. The precipitate was filtered off and extracted with 260 cc. of cold distilled water. A 25 cc. quantity of the latter solution was evaporated under diminished pressure to 5 cc. and injected intraperitoneally into 2 mice in 1.5 cc. portions without undue distention of the abdomen. Both mice died in less than twelve hours. The remaining 2 cc. when boiled gave no coagulum, showing the absence of heat-coagulable protein. Then 235 cc. of the water extract was precipitated with 5 volumes of 95 per cent alcohol and allowed to stand overnight. The small white precipitate which formed was thrown down in the centrifuge, and the supernatant liquid was discarded. The precipitate was dried over phosphorus pentoxide in vacuo. It weighed 0.28 Gm. after drying and possessed the following properties:

A quantity weighing 0.28 Gm. dissolved slowly in 9 cc. of water to form a clear brown-tinged solution, which gave a positive Molisch reaction, a weak biuret reaction and no reaction in the Hopkins-Cole, benzaldehyde and Ehrlich diazo tests. It gave no apparent reaction with nitrous acid and did not pass through a collodion membrane. The solution yielded a precipitate on half saturation with ammonium sulfate. This solution injected into 5 mice in 12, 16, 20, 24 and 28 minim portions caused death in less than twelve hours in all the animals. The fatal dose for a 20 Gm. mouse is therefore less than 23 mg.

The Alcoholic Filtrate.—The alcoholic filtrate from precipitation by alcohol of the 235 cc. of original loop fluid mentioned in a foregoing paragraph was evaporated at room temperature under diminished pressure to a thick orange-colored paste, diluted with a small portion of distilled water and again evaporated very nearly to dryness. This procedure was repeated three times to insure complete removal of the alcohol. The volume of the solution was finally adjusted with distilled water to 4 cc. This final solution was a light orange-yellow colloidal one, not cleared by strong centrifuging nor by filtering. Mice receiving 1 cc. doses of this solution intraperitoneally died in four to five minutes, apparently from asphyxia. They ran and leaped about the cage, presenting symptoms of muscular spasm and convulsions. This toxic fraction gave a very strong diazo reaction. The study for histamine in the specimen was done by Kossel's method for the basic amino acids. The alcoholic filtrate was evaporated to small volume, diluted to 50 cc. with distilled water and hot saturated silver sulfate added until an excess of silver was present. The solution was then saturated with powdered barium hydroxide, the precipitate removed and suspended in dilute sulfuric acid, and the silver removed with hydrogen sulfide. The silver sulfide was removed, the filtrate saturated with hot silver sulfate, excess barium carbonate added and the solution boiled. The precipitate which formed on boiling was removed and freed from silver in the usual manner. This filtrate gave a weak diazo reaction but

gave no reaction for histidine by the method of Kapellar and Adler. The positive diazo reaction indicated that histidine was present. (Certain bile acids, however, also will give a positive diazo reaction. The Kapellar-Adler test is specific for histidine but is not extremely sensitive. We believe that histidine was present, but not in sufficient quantity to give the Kapellar-Adler reaction.)

A 50 cc. quantity of the original loop fluid, solution A, was boiled, centrifuged, and filtered and the filtrate poured into 5 volumes of 95 per cent alcohol. The precipitate which formed was filtered off and dissolved in water and again precipitated with alcohol. The precipitate was white, fluffy and larger than that secured from the same amount of loop fluid by the "cold procedure." This precipitate dissolved in water and concentrated was injected into 2 mice in 1.5 cc. portions. Both died in twelve hours or less. The solution gave a positive Molisch reaction and a weak biuret reaction; the Hopkins-Cole and benzaldehyde tests were negative. (This white precipitate is apparently about the same in character as that secured by the cold process.)

STUDIES OF THE CHEMICAL CHARACTER AND TOXICITY OF THE LOOP FLUID FORMED IN THE ABSENCE OF BACTERIA

On Aug. 16, 1940, 4 dogs were anesthetized with ether, and in each approximately 30 inches of the lower part of the ileum, to within 2 inches of the cecum, was isolated. All arteries, veins and lymphatics to each loop were completely closed with ligatures. The loop ends were opened and running tap water directed through the loop without excessive pressure, until the return was completely clear. The loop was then stripped dry and about 1 cc. of tincture of merthiolate per inch of loop instilled. The tincture of merthiolate was left in the loop twenty minutes and was then washed out with running tap water until the return was perfectly clear. The loop was then stripped and the loop ends closed and returned to the abdomen.

In four to four and a half hours the abdomen was reopened without anesthesia or medication and the loop contents collected in a sterile beaker. Smears were made immediately, and in those from 3 specimens no micro-organisms were seen. In that from the fourth specimen there were 12 gram-positive micro-organisms, morphologically *Cl. welchii*, per oil immersion field. This specimen was discarded from chemical analysis.

As controls, 3 mice were given 8 minim doses of the contents of each of the four loops by intraperitoneal injection. The 3 mice which received doses of the specimen in which the bacteria were seen were all found dead next morning. Of the 9 mice which received doses of the specimens that showed no bacterial content on smear, only 1 died.

The total of the loop material from 2 of the dogs which showed no bacteria on smear was not treated with heat. It was diluted 1:1, promptly centrifuged and precipitated with alcohol exactly as outlined in the section entitled "Chemical Studies on Toxins Formed in the

Presence of Bacteria" (p. 831). The same chemical analyses and procedures as outlined there were used in the study of this specimen, and the same results were obtained with the following notable exceptions:

The Alcoholic Filtrate.—This term has the same connotation here as in connection with the chemical studies of toxins formed in the presence of bacteria (p. 832). Ehrlich's diazo test was absolutely negative on this alcoholic filtrate. This was conclusive evidence that no histamine was present.

The alcohol-soluble product from the intestinal loops of the 2 dogs was adjusted with distilled water to a final volume of 30 minims. A 1 cc. and a 14 minim (0.85 cc.) dose of this slightly muddy amber-colored solution from which all alcohol had been removed were injected intraperitoneally into 2 mice, respectively, on August 19.

About two minutes after the injection of the 14 minim dose, the mouse presented some labored respiration, seemingly a general tightening of all muscles of the body and some increase in excitability. The reaction was similar to, perhaps, but much milder than, the reactions seen in the animals which had previously been given an alcohol-soluble toxic fraction as mentioned in the previous section. The injection was made at 5:50 p. m. At 6:15 p. m. the mouse was leaning to the left side and moved gradually in a circle to the right about the cage. This reaction persisted for thirty minutes or more. At 6:30 p. m. the animal was quite ill and lethargic. The next morning (August 20) at 9:30 a. m. the animal was excitable, and when the cage was tapped lightly it went into a general spasm with only mild convulsions and appeared dead for a few seconds but then became active again. Both left extremities continued to be partially paralyzed. The animal was found dead at 8 a. m., August 21.

The second mouse was given the 1 cc. dose of the fraction at 5:45 p. m. on August 19. The animal showed some slightly labored respiration and moderately increased excitability. At 6:15 p. m. it was rather quiet, and at 6:25 p. m., after two or three very labored respiratory cycles, it died rather quietly. This animal showed no manifestations of paralysis or convulsions.

Fractions Precipitated by Alcohol.—This term likewise is synonymous with that in the section on toxins formed in the presence of bacteria. The feathery-like white alcoholic precipitate which was collected and treated by the method outlined in that section (p. 831) was isolated.

The feathery-like precipitate to alcohol was the same in appearance as the product obtained and described in that section. However, only 0.06 Gm. of the material was obtained. This was only a fifth to a third of the total amount which had been obtained in the same experiment of

that section as compared proportionally to the amount collected from 2 dogs in that experiment. This material was dissolved in distilled water.

A 1.5 cc. dose of this solution was injected into each of 4 mice, this dose giving 0.018 Gm. of the isolated product. (This was approximately the same dose as used in the injection of the product which had been formed in the presence of bacteria, as set forth in the previous section.)

The solution was injected into mice on August 19. None of these mice died. None appeared especially ill after the injections. All were active the next morning.

COMMENT

The numerous and repeated observations made during the studies outlined in parts I and II of this paper warrant some definite conclusions. Certainly very toxic substances are formed from the tissues of the wall of the strangulated small intestine in the presence of bacteria, irrespective of gross substances normally found within the lumen of the intestinal tract. These toxic substances are formed early, being present in quite appreciable quantities within three to four hours after strangulation has occurred. No studies relative to the mechanics of absorption of such substances have been made here, but work of previous investigators and of the senior author (J. K. D.), together with a practical consideration of the problem of obstruction in the human being, leaves no doubt that such substances may be absorbed into the general system.

Previous workers have concluded that bacteria are essential to the production of toxins from the intestinal wall itself, and though we cannot go so far as to use the word "essential," our studies certainly confirm the opinion that if bacteria are not essential to the production of such toxins, they nevertheless enhance the rapidity of toxin formation considerably. *B. perfringens* antitoxin (Lilly) does not neutralize the toxic substances.

A most consistent reaction was produced in our animals by an injected toxin which caused lethargy and evident general depression of the animal, with death in about twenty-four hours. Studies not described in this paper, which were made on rats with toxic but not fatal doses of our products, have occasionally demonstrated paralysis of some of the motor nerves (and possibly degeneration of the optic nerve, though this probably is not established with certainty).

The second type of reaction which occurred in our animals, from another isolated toxic fraction, was death occurring within one to five minutes after intraperitoneal injection of the toxin, preceded by markedly labored respiration, marked excitement and apparently asphyxia, these pharmacologic reactions being similar to those produced by histamine.

The toxic fraction causing the latter reaction is found in much smaller quantities than the toxin producing the slower reaction.

Protein chemistry is a specialty within itself, there being probably thousands of protein compounds which have not been accurately identified structurally. Any chemical attempt to identify most protein compounds structurally must in itself initially alter many of the compounds in such a way that their exact structural recapitulation becomes most difficult after the first step of a chemical study.

We are not justified in assuming from our work that we have made accurate identifications of our toxic substances. We should like to believe the substances are split products of protein degeneration, the degeneration being enhanced by proteolytic bacteria. Other workers have asserted that the toxic substances are proteoses. Certain parts of our chemical studies indicate that primary and secondary proteoses are the toxic substances. And yet though our work has been as extensive as that of some investigators who have claimed identification of proteoses, we do not feel justified in making the broad assertion that proteoses are the primary toxic factors. In fact a toxin, these studies indicate, belonging chemically to the class of carbohydrates has been repeatedly identified by the consistent appearance of the positive Molisch reaction. So, though we are justified in the conclusions that follow, more intensive study on toxins procured by our method or one similar, a method which does isolate in the beginning very markedly toxic products, which are formed early in the strangulating intestinal wall, is indicated before physicians can accept the statement that a positive identification of any toxin has been made.

Clinically, in the majority of cases of fatal obstruction in man, there is interference with the blood supply to the intestinal wall either directly by strangulation or secondarily by distention. Therefore every effort should be made to determine as accurately as possible the exact nature of the toxins produced by interference with the blood supply in the hope that, as a subsequent step, some neutralizing agent can be found.

SUMMARY OF PARTS I AND II WITH CONCLUSIONS

Thin, relatively clear, untreated, nonsterile, fresh, normal ileac secretion from dogs is not lethal to mice when injected in relatively large doses (8 minims) intraperitoneally, provided the bacterial content of the fluid is low (arbitrarily below 8 to 10 micro-organisms per oil immersion field).

As demonstrated in part I, the sterile filtrate of loop fluid from the walls of degenerating ilea of dogs becomes lethal to mice in two and a half hours or less after strangulation of the arterial blood supply to the loops.

Our principal toxic substances injected intraperitoneally into mice in about minimum lethal doses gave a consistently characteristic reaction. The reaction is one of lethargy and evident general depression, with death occurring in twenty-four hours or less after the injection.

Two fractions are obtained from the principal substances giving the toxic reaction just described, and each of the two fractions causes the same type of depressive reaction when injected into mice. One of the fractions is water soluble, is coagulated or destroyed by heat and contains roughly 85 per cent of the total toxicity of the whole of the fresh substance obtained from the strangulated intestinal wall. The second toxic fraction is water soluble and is not destroyed by heat.

Another toxic fraction is soluble in alcohol and water, is not destroyed by heat, is produced in small quantities and gives a rapidly fatal death when injected into a mouse. Death occurs in one to five minutes after the injection and is preceded by excitement, muscle spasm and rigidity and apparent asphyxia, a reaction very similar to, if not exactly, that produced by histamine. We believe this toxic substance is histamine or a very similar substance.

Practically all the toxic substances that we isolated were produced in the presence of bacteria. Only a small amount of a toxic substance soluble in alcohol and water (not histamine) was isolated from strangulated intestine in the absence of bacteria. This small bit of substance was lethal to mice, however, though producing death less rapidly than the histamine or histamine-like fraction.

Polyvalent *B. perfringens* antitoxin does not counteract the toxins we produced.

One of the main reasons why so much confusion remains regarding the problem of intestinal obstruction is that research workers have generalized too broadly on the secondary factors in the morbid picture of intestinal obstruction.

It has been repeatedly proved that nothing will save the patient unless the strangulated intestinal tissue is removed when this is a factor in obstruction. It has also been accepted that death of intestinal tissue occurs not only from direct strangulation but from distention alone.

We followed a method of experimentation which procures fresh toxic substances from a strangulated intestinal wall. We have demonstrated that these principal toxic substances are not found by our method of experimentation in the absence of bacteria but are produced quite rapidly (within two to four hours) in appreciable quantities in the presence of proliferating bacteria.

Despite rather extensive investigation, the difficulties of chemical analysis of protein compounds make us reluctant to identify the principal substances as proteoses, though some of our tests indicate that they are

primary and secondary proteoses. However, a substance giving a positive reaction in the Molisch test for carbohydrates is present.

Repeated investigations with the toxic substances obtained by our method or similar methods should be carried out by investigators in an attempt to identify more accurately the toxins which we have found by the methods described. If these toxins could be more accurately identified, it might be possible to find a neutralizing agent for them and thereby make an important contribution to the therapy of obstruction.

Prof. Howard Reynolds, of the University of Arkansas, reviewed the results of the chemical studies in the absence of Mr. Lewis. Drs. J. G. Wahlin, C. H. McDonald, Paul L. Day, of the departments of bacteriology, physiology and pharmacology, and physiological chemistry, respectively, gave helpful suggestions. Eli Lilly & Company (at the request of Dr. E. G. Stewart and Mr. J. E. Hoffmeister) supplied the freshly prepared *B. perfringens* antitoxin and the solutions of merthiolate used in the investigation.

HODGKIN'S DISEASE

REVIEW OF FIFTY-FOUR CASES

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Since Thomas Hodgkin's ¹ report in 1832 of 7 cases in which there was presented a syndrome of swelling of the superficial lymph nodes and enlargement of the liver and spleen with anemia, followed by cachexia and death, many similar reports have appeared in the literature. Hodgkin did not affix a name to the disease; this was left to Wilks,² who in 1865 recorded 15 similar cases and applied the name Hodgkin's disease. Not all of Hodgkin's original 7 cases are considered to present true examples of the disease. Wilks,² Reed,³ Halsted⁴ and Fox⁵ expressed the opinion that only 2 to 4 of the cases offer true examples of the disease process, the others being cases of tuberculosis, syphilis and leukemia.

The monumental work of Sternberg⁶ (1898) and Reed³ (1902) did much to clarify the histologic picture and pathologic behavior of the disease. Both gave excellent descriptions and appended good drawings and sketches, placing particular emphasis on the occurrence of the large giant endothelial cells which carry their names. Wallhauser⁷ found about fifty synonyms for the disease, indicating considerable confusion as to classification and causation, although the histologic and the pathologic pictures have remained clear for forty years.

The theories of causation have varied from an infectious to a neoplastic basis, with many holding to an entity midway between.

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1. Hodgkin, T.: *Med.-Chir. Tr.*, London **17**:68, 1832; reprinted, *M. Classics* **1**:742, 1937.

2. Wilks, W.: *Guy's Hosp. Rep.* **9**:56, 1865.

3. Reed, D.: *Bull. Johns Hopkins Hosp.* **10**:133, 1902.

4. Halsted, W. S., cited by Jones, G. W.: *Ann. M. Hist.* **2**:471, 1940.

5. Fox, H.: *Guy's Hosp. Rep.* **86**:11, 1936.

6. Sternberg, C.: *Ztschr. f. Heilk.* **19**:21, 1898.

7. Wallhauser, A.: *Hodgkin's Disease*, *Arch. Path.* **16**:522 (Oct.) 1933.

Sternberg⁶ expressed the belief that the disease is an atypical form of tuberculosis, although this was opposed vigorously by Reed,⁸ who maintained the process is an infective granuloma of unknown cause. Fraenkel and Much⁸ (1910) and Bunting and Yates⁹ (1913) reported that they found specific causative organisms.

Gordon¹⁰ in 1932 described a test, positive in 70 per cent of the cases, which consisted of intracerebral injection of a broth suspension of diseased lymph nodes into rabbits and guinea pigs. A syndrome consisting of spastic paralysis, ataxia, retraction of the head, fits and loss of weight was produced. He was convinced that a virus was responsible for the disease. In 1938, four different workers¹¹ showed that the eosinophils in tissue affected by Hodgkin's disease were responsible for the encephalitic reaction of the animals and that the same reaction can be produced by other tissues containing eosinophils. The Gordon test is a valuable confirmatory test when accompanied by histologic examination, as shown recently by Steiner,¹² who found the test positive in 73.9 per cent of 299 recorded cases of histologically proved Hodgkin's disease and falsely positive in only 1.77 per cent of 452 control cases.

In 1939 Parsons and Poston¹³ reported a group of 4 cases of human brucellosis in which the histologic study of lymph nodes and autopsy material revealed the characteristics of typical Hodgkin's disease. Recently at the same hospital Forbus and Gunter¹⁴ studied autopsy material from 4 additional cases of typical Hodgkin's disease, with recovery of the *Brucella* organism in all. Poston and Parsons¹⁵ reported cultures of *Brucella* from the lymph nodes of 10 of 19 patients with Hodgkin's disease.

The present paper analyzes 54 cases of histologically proved cases of Hodgkin's disease observed at the University of Virginia Hospital in the past fifteen years. Biopsy was performed in 51 cases and autopsy

8. Fraenkel, E., and Much, H.: *Ztschr. f. Hyg. u. Infektionskr.* **67**:159, 1910.

9. Bunting, C. H., and Yates, J. L.: *Cultural Results in Hodgkin's Disease*. *Arch. Int. Med.* **12**:236 (Aug.) 1913.

10. Gordon, M. H.: *Rose Research on Lymphadenoma*, Bristol, John Wright & Sons, Ltd., 1932.

11. Edward, D. S.: *Lancet* **1**:936, 1938. King, D. P.: *St. Thomas's Hosp. Rep.* **3**:68, 1938. McNaught, J. B.: *Gordon Test for Hodgkin's Disease: Reaction to Eosinophils*, *J. A. M. A.* **111**:1281 (Oct. 1) 1938. Turner, J. C.; Jackson, H., Jr., and Parker, F.: *Am. J. M. Sc.* **195**:27, 1938.

12. Steiner, P. E.: *Reliability and Significance of Gordon Test in Hodgkin's Disease*, *Arch. Path.* **31**:1 (Jan.) 1941.

13. Parsons, P. B., and Poston, M. A.: *South. M. J.* **32**:7, 1939.

14. Forbus, W. D., and Gunter, J. U.: *South. M. J.* **34**:376, 1941.

15. Poston, M. A., and Parsons, P. B.: *J. Infect. Dis.* **66**:86, 1940.

in 4. About 20 other cases were not included because the histologic changes were inconclusive or the diagnosis was merely clinical. One case in which Hodgkin's disease was diagnosed on biopsy of a cervical lymph node is omitted; this will be reported separately,¹⁶ as the patient died three months later of generalized torulosis.

INCIDENCE

Race.—Hodgkin's disease has been reported to attack every race and nearly all nationalities. The reports of cases in America indicate that the distribution has been predominantly among the white and American born. Goldman¹⁷ reported an incidence of 6.6 per cent Negroes in a group of 212 patients with Hodgkin's disease.

In our series the condition occurred in 45 white persons (83.3 per cent) and 9 Negroes (16.7 per cent). Over a period of many years the average admission rate of Negroes at this hospital has been 15.6 per cent.

Sex.—The disease is more prevalent in men than in women. Wallhauser⁷ collected 1,447 cases from the literature and found the incidence to be 70 per cent in men and 30 per cent in women.

In our group there were 32 men (59.3 per cent) and 22 women (40.7 per cent).

Age.—Hodgkin's disease may occur at any age. Smith¹⁸ collected 5 cases in which the onset was before the sixth month of age. A number have been recorded in which the condition developed in the seventh and eighth decades of life. In the greatest number of cases the onset occurred in the third decade of life.

The youngest patient in our series was 4 and the oldest 70. The greatest number of the patients were in the third decade of life; the incidence of the disease was fairly well distributed over the other decades except the sixth, in which it was low, and the seventh, in which it was higher than in any except the third (chart).

PREDISPOSING FACTORS AND POSSIBLE CAUSES

There were no demonstrable predisposing factors in any of the cases studied. Heredity, environment, occupation and food appeared to play no important part. The majority of the patients were ward patients, but there were 2 physicians' wives and 1 hospital intern in

16. Morton, C. B.; Derrick, W. A., and Burger, R. E.: *Torula Infection: A Review and Report of Three Cases*, to be published.

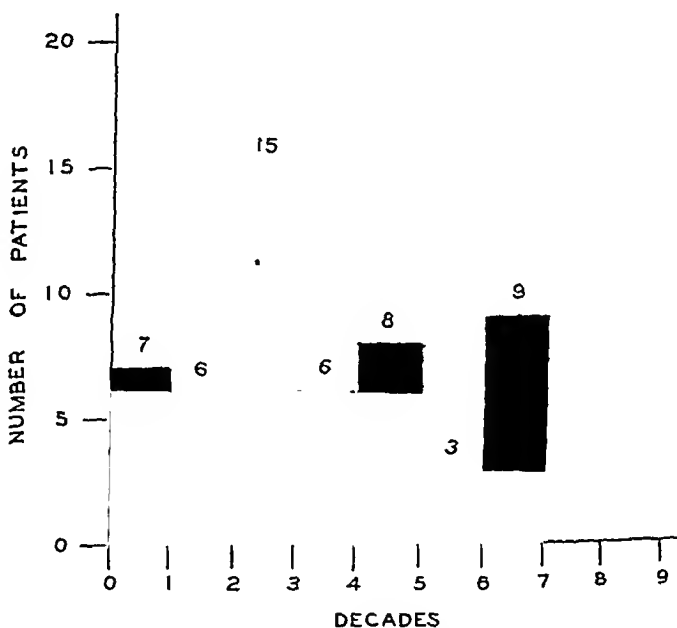
17. Goldman, L. B.: *Hodgkin's Disease: Analysis of Two Hundred and Twelve Cases*, J. A. M. A. **114**:1611 (April 27) 1940.

18. Smith, C. A.: J. Pediat. **4**:12, 1934.

the group. There was no familial history of Hodgkin's disease. McHefhey and Peterson¹⁹ reported the occurrence of Hodgkin's disease in 2 brothers almost simultaneously.

Roentgenograms of the chest in 3 cases revealed scarring and calcification consistent with old healed tuberculosis; in 3 additional cases there was suspicion of activity, and in 1 case there was death from concomitant pulmonary and miliary tuberculosis and Hodgkin's disease. Thus in 12.9 per cent of the cases there was healed or active tuberculosis.

Of the 54 cases, cultures of the blood were made in 3 and of the lymph nodes in 2. In 1 case the culture of the blood was positive for *Brucella*.



Age incidence in 54 cases of Hodgkin's disease.

CHIEF COMPLAINTS AND SYMPTOMS

Swelling of the glands of the neck, weakness, fatigue, loss of weight, cough, dyspnea and backache were the commonest complaints on admission to the hospital. Table 1*A* records the chief complaint and table 1*B* the symptoms present on admission in 44 cases; in 10 cases there were no symptoms except the swelling of glands.

The average time between the onset of symptoms and entry into the hospital in 52 cases was ten and one-half months. There was no record of the duration of the disease before admission in 2 cases.

19. McHefhey, G. J., and Peterson, R. F.: Hodgkin's Disease Occurring Simultaneously in Two Brothers, *J. A. M. A.* **102**:521 (Feb. 17) 1934.

TABLE 1.—*Chief Complaints and Symptoms in Cases of Hodgkin's Disease*

A. The Chief Complaint That Brought 54 Patients to the Hospital			B. The Most Common Symptoms Prior to Hospitalization in 44 Cases (In 10 Cases There Were No Symptoms)		
Complaint	Patients	Per Cent	Common Symptoms	Cases	Per Cent
Swelling of the glands of the neck.....	31	57.1	Weakness.....	26	48.2
Fatigue and weakness.....	5	9.3	Loss of weight.....	19	35.2
Pain in the back and the legs.....	5	9.3	Cough.....	13	21.1
Cough, dyspnea and sore throat.....	3	5.6	Fatigue.....	9	16.6
Abdominal pain.....	3	5.6	Anorexia.....	8	14.8
Mass in the abdomen.....	2	3.7	Pain in the back and the legs...	8	14.8
Generalized superficial glandular enlargement.....	1	1.8	Malaise.....	7	12.9
Enlargement of the inguinal glands.....	1	1.8	Nervousness.....	6	11.1
Pain in the eyes and head.....	1	1.8	Edema.....	6	11.1
Cutaneous lesions.....	1	1.8	Dyspnea.....	5	9.3
Tuberculosis.....	1	1.8	Fever.....	5	9.3
			Headache.....	4	7.1
			Abdominal pain.....	4	7.1
			Nausea and vomiting.....	3	5.6
			Night sweats.....	2	3.7
			Sore throat.....	2	3.7
			Pain in the neck.....	2	3.7
			Pruritus.....	2	3.7

CLINICALLY OBSERVED LOCALIZATION

Although the disease is usually generalized, with widespread involvement of the reticuloendothelial system, definite areas of localization are observed clinically. A characteristic of the disease in the early stages is that unilateral lymphatic areas are attacked more frequently than symmetric areas. The lymph nodes of the neck were involved first in two thirds of the cases. Table 2A gives the regions first involved in this group, determined by palpation, roentgenograms and surgical exploration. Table 2B gives the frequencies of involvement of lymph nodes, tissues and organs during the course of the disease.

Mediastinum.—Involvement of the mediastinum, as evidenced in roentgenograms by widening, nodular protrusions of enlarged glands and actual infiltration of the lungs, was present in 55.5 per cent of the cases. In 2 cases the mediastinal nodes were apparently the first of the body structures to be involved. There was involvement of mediastinal nodes in all 4 of the patients who came to autopsy.

Stomach.—Sherman²⁰ in 1938 collected 75 cases of Hodgkin's disease in the gastrointestinal tract from the literature, and in about a third of these cases there was involvement of the stomach.

The stomach and regional lymph nodes were involved in 2 cases of our series. In each instance a roentgenogram revealed a large filling defect in the stomach, and at exploration a large mass was found in the stomach, with involvement of regional lymph nodes. These were thought to be cases of inoperable carcinoma till biopsy of the regional nodes revealed Hodgkin's disease.

Spleen.—During the course of the disease the spleen was observed clinically to be enlarged in 33.3 per cent of the cases. Of the 4 patients who came to autopsy, 3 had involvement of the spleen, and 2 of these had palpably enlarged organs.

Desjardins and Ford²¹ (1923) noted splenomegaly in only 14.9 per cent of 135 cases. Boyd²² stated that 75 per cent of the cases show splenomegaly.

Liver.—The liver was palpable in 20 (37 per cent) of the cases. This is somewhat lower than the 60 per cent given by Ziegler²³ and

20. Sherman, E. D.: Gastro-Intestinal Manifestations of Lymphogranulomatosis (Hodgkin's Disease), Arch. Int. Med. 61:60 (Jan.) 1938.

21. Desjardins, A. V., and Ford, F. A.: Hodgkin's Disease and Lymphosarcoma, J. A. M. A. 81:925 (Sept. 15) 1923.

22. Boyd, W.: The Pathology of Internal Diseases, Philadelphia, Lea & Febiger, 1934.

23. Ziegler, K.: Die Hodgkinsche Krankheit, Jena, Gustav Fischer, 1911.

TABLE 2.—Cases in Which Involvement of Certain Organs Was Shown

A. Region First Involved			B. Region Involved at Some Stage of the Disease		
Organ or Nodes	Cases	Per Cent	Organ or Nodes	Cases	Per Cent
Left cervical nodes.....	15	27.8	Left cervical nodes.....	44	81.5
Right cervical nodes.....	14	25.9	Right cervical nodes.....	37	63.5
Cervical nodes on both sides.....	7	12.9	Axillary nodes.....	27	50.0
Inguinal nodes.....	6	11.1	Inguinal nodes.....	20	37.0
Axillary nodes.....	3	5.6	Epitrochlear nodes.....	1	1.8
Abdominal nodes, liver and spleen.....	3	5.6	Mediastinum.....	30	55.5
Generalized superficial glands.....	2	3.7	Liver.....	20	37.0
Mediastinum.....	2	3.7	Spleen.....	19	35.2
Stomach and regional nodes.....	2	3.7	Abdominal nodes.....	8	14.8
			Stomach and regional nodes.....	2	3.7
			Bone.....	4	7.4
			Skin.....	2	3.7
			Eye and retrobulbar tissues.....	2	3.7

the 50 per cent given by Boyd.²² The liver was involved in 2 of the 4 cases in which there was an autopsy and in 1 in which surgical exploration was done. There was clinical icterus in 2 (3.7 per cent) of the cases; this was in agreement with 4.2 per cent in Goldman's¹⁷ 212 cases.

Skin.—Cutaneous involvement was proved histologically in 2 cases. In the first it was associated with generalized superficial glandular enlargement; in the second, with involvement of the liver proved by biopsy. Puritus was present during the course of the disease in 10 (18.5 per cent) of the cases. .

Bone.—In 4 of the cases (7.4 per cent) there was roentgen evidence of osseous involvement. Goldman¹⁷ reported osseous involvement in 6.6 per cent of 212 cases and Craver and Copeland²⁴ in 15.7 per cent of 172 cases. The bones involved in our series were more commonly the vertebrae, less often the pelvic bones, sacrum and ribs. Biopsy of involved bone of 2 of the patients showed tissue typically affected by Hodgkin's disease. Three other patients complained of moderately severe pain in the back and hips at some time during the course of the disease, but roentgenograms were never taken.

BLOOD PICTURE

Opinions as to the blood picture in Hodgkin's disease differ widely. Bunting²⁵ emphasized certain changes in the blood count and blood smear, but these are variable. Steadily progressive anemia of the hypochromic type is usually found. In this series 32 (59.3 per cent) patients had a leukocyte count above 8,000. The two highest leukocyte counts were 68,300 and 54,000, with polymorphonuclears predominant; eosinophils were not present in the blood smear in the first instance and were 2 per cent in the second. In both the leukocytosis was accompanied by rather severe secondary anemia. Both the patients had superficial glandular enlargement plus bony involvement. The leukocyte count of 1 patient receiving no treatment was 2,600. Five patients receiving roentgen therapy had their previously normal leukocyte counts depressed below 4,000. The leukocyte counts of the remainder of the patients were within the normal range.

Eosinophilia has long been stressed as a characteristic finding. Goldman¹⁷ and Baker and Mann²⁶ observed eosinophilia in 20 per cent of their cases. In our series there was eosinophilia (5 per cent

24. Craver, L. F., and Copeland, N. M.: Changes in Bone in Hodgkin's Granuloma, Arch. Surg. 28:1062 (June) 1934.

25. Bunting, C. H.: Bull. Johns Hopkins Hosp. 25:173, 1914.

26. Baker, C., and Mann, W. N.: Guy's Hosp. Rep. 89:83, 1939.

or more) in 20.3 per cent of the cases. The highest was 25 per cent, in the case of Hodgkin's disease of the skin associated with superficial glandular disease.

OCCURRENCE OF FEVER

In 1887 Pel²⁷ and Ebstein²⁸ described periodic bouts of fever with remissions in the disease process. Of the 54 patients in our series, all but 5, whose disease was in an early stage, were pyrexia when observed. A continued or swinging pyrexia with temperatures from 100 to 104 F. was much more common than the classic Pel-Ebstein variety, which occurred in only 8 (14.8 per cent) of the patients under observation.

DURATION OF LIFE

Hodgkin's disease may be rapidly fatal or slowly progressive. Two of the patients whose disease ran the shorter course lived about three months after the onset of symptoms; the patient who lived longest died eight years, eight months after the onset. The average duration of life of 41 patients followed up and known to be dead was twenty-six months, dating from the onset of symptoms. Four patients are thought to be dead, but a follow-up could not be obtained. Nine patients known to be alive have been living an average of twenty-nine and five-tenths months at the time of writing. In Goldman's¹⁷ 212 cases the average duration of life was about thirty-two months; in Baker and Mann's²⁶ 65 cases it was about eighteen months. Craver²⁹ reported periods of survival of five years or more in 12 per cent of 125 proved cases of Hodgkin's disease. In our series 3 patients (5.6 per cent) are known to have lived longer than five years.

SECONDARY CAUSES OF DEATH

In 28 of the known fatal cases the mode of death is known and is given in table 3.

Terminal exhaustion, anemia and pyrexia were mentioned most often, being present in 21 cases.

Death due to respiratory failure with signs of pulmonary disease or mediastinal compression occurred in 6 cases. One patient died on the operating table shortly after an attempt to decompress the mediastinum because of marked respiratory difficulty.

In 1 case there were concomitant Hodgkin's disease and pulmonary and milary tuberculosis.

27. Pel, P. K.: *Berl. klin. Wchnschr.* **24**:644, 1887.

28. Ebstein, W.: *Berl. klin. Wchnschr.* **24**:565, 1887.

29. Craver, L. F.: *Am. J. M. Sc.* **188**:609, 1934.

In many there was overlapping of the terminal symptoms, and it was rather difficult to select the cause of death.

RESULTS OF TREATMENT

The methods of treatment in this series of cases are given in table 4. The larger number of the patients (41) were given roentgen therapy alone to the involved areas. A few had surgical or radium treatment alone; 2 had combined surgical and roentgen therapy, and 5 received no treatment.

In the group known to be dead the average duration of life was much greater in those receiving treatment, regardless of the type of

TABLE 3.—*Mode of Death in Twenty-Eight Cases of Hodgkin's Disease*

Type	Cases	Per Cent
Respiratory failure.....	6	21.4
Exhaustion, anemia and pyrexia.....	21	75.0
Miliary tuberculosis.....	1	3.6

TABLE 4.—*Results of Treatment **

Type of Therapy	Patients (41) Known to Have Died		Patients (9) Still Alive	
	Patients	Average Length of Life (Mo.)	Patients	Average Living Time at Time of Writing (Mo.)
Roentgen alone.....	30	28.1	9	29.5
Surgical alone.....	5	28.2
Radium alone.....	1	30.0
No treatment.....	5	10.4

* Of the patients who were not followed up, 2 received roentgen therapy alone and 2 combined surgical and roentgen therapy.

therapy, than in those not receiving treatment. Those receiving some form of therapy lived twenty-eight to thirty months; those not receiving treatment lived only ten and four-tenths months.

In 9 living patients receiving repeated irradiation of involved tissues the duration of life at the time of writing was already twenty-nine and five-tenths months. Roentgen irradiation of the entire lymphatic system has not been tried at this hospital. Blood transfusions and general therapeutic measures have been valuable adjuvants in building up the patients.

Most roentgen therapists use repeated local application of irradiation. Jacox, Peirce and Hildreth³⁰ in surveying the clinical result-

30. Jacox, H. W.; Peirce, C. B., and Hildreth, R. C.: *Am. J. Roentgenol.* 36:165, 1936.

of this form of treatment in 161 cases of Hodgkin's disease over a decade, were convinced that roentgen therapy induced definite extension of life and that systemic irradiation was proving more effectual in prolonging life than repeated local irradiation.

Regardless of the type of therapy, Hodgkin's disease has proved an almost universally fatal malady in the proved cases. There are a few isolated reported cures, but as to most of these there is a question of correct diagnosis or of adequate follow-up. A few cases have been reported in which the patient lived twenty years or more, and Jackson³¹ recorded a case in which there was recurrence of nodes removed surgically after a lapse of twenty-six years.

SUMMARY

We have analyzed 54 cases of histologically proved Hodgkin's disease seen at the University of Virginia Hospital in the past fifteen years. In discussing the clinical features, we have compared our figures with others occurring in the literature.

No data relating to causation are presented. In 1 case among 3 studied by culture of the blood, *Brucella* was isolated.

Enlargement of the cervical glands is commonly the first sign and is followed later in most instances by involvement of superficial and mediastinal nodes, accompanied by swinging or sustained pyrexia, usually not of the Pel-Ebstein type.

The average time of survival from the onset of the first symptom was twenty-six months. Treatment in most cases consisted of repeated roentgen irradiation of involved tissues aided with blood transfusions and general therapeutic measures. Treated patients have on the average survived nearly three times as long as untreated patients.

Dr. W. Ansell Derrick, of the department of pathology of the University of Virginia, assisted in reviewing the histologic slides.

31. Jackson, H., Jr.: *M. Clin. North America* 21:361, 1937.

PREOPERATIVE MANAGEMENT OF GASTROJEJUNOCOLIC FISTULA

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The immediate mortality rate after surgical intervention in the treatment of well developed gastrocolic fistula is disturbingly high, and yet the prognosis for the disease if treated by medical means alone is exceedingly poor. Nearly all patients treated medically die of progressive inanition, avitaminosis or intercurrent infection. Verbrugge¹ reported a series of 20 cases in which 5 patients died after operation; the mortality rate was thus 25 per cent. Loewy² collected reports of 63 cases; the operative mortality rate in this group was 27 per cent. Allen³ reported 8 cases with 2 deaths; Lahey and Swinton⁴ reported an immediate mortality rate of 63 per cent in 8 cases and Rife⁵ a mortality rate of 20 per cent in 14 cases. A high mortality rate seems to accompany any type of operation performed in one stage, regardless of the technic employed or the quality of the postoperative management.

The first report of a spontaneous communication between the stomach and the colon was made by Haller⁶ in 1755. Prior to 1903, when Czerny² reported the first case of gastrojejuncolic fistula after gastroenterostomy, in most of the 70 cases reported the anomaly was caused by carcinoma of the stomach or the colon. Since that time the increasing use of gastroenterostomy in the treatment of duodenal ulcer has resulted in the establishment of a communication from the stomach to the jejunum and colon in many cases. When such a fistula occurs now, it is usually presupposed that gastroenterostomy has been performed—in most cases, years before for benign duodenal ulcer—and that an eroding, adherent gastrojejunal ulcer developed. Such a communication

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1. Verbrugge, J.: *Gastrojejuncolic Fistulas*, Arch. Surg. **11**:790-808 (Nov.) 1925.

2. Cited by Pfeiffer and Kent.¹¹

3. Allen, A. W.: *An Aseptic Technic Applicable to Gastrojejuncolic Fistula*, Surgery **1**:338-348 (March) 1937.

4. Lahey, F. H., and Swinton, N. W.: *Gastrojejunal Ulcer and Gastrojejuncolic Fistula*, Surg., Gynec. & Obst. **61**:599-612 (Nov.) 1935.

5. Rife, C. S.: *Gastrojejuncolic Fistula*, Am. J. Surg. **40**:73-88 (April) 1933.

6. Haller, cited by Tynes, A. L., and Cole, F. L.: *Gastrojejuncolic Fistula with Report of Three Cases*, Mil. Surgeon **86**:113-121 (Feb.) 1940.

after gastroenterostomy for gastric ulcer is rare and seldom occurs in women. Gastrojejunocolic fistula apparently occurs in 0.1 to 0.2 per cent of the cases in which gastroenterostomy is performed and in about 10 per cent of the cases in which gastrojejunal ulcer develops.

PURPOSE AND MATERIAL OF STUDY

It is the purpose of this study to present a review of 49 consecutive cases of well developed gastrojejunocolic fistula in which operation was performed at the Mayo Clinic from 1930 to 1939, inclusive. Cases of so-called impending fistula are not included. All operations were performed in one stage, but many different types of corrective measures were used; these have been described by Walters and Clagett.⁷ Besides the one stage operation, the only other constant factor in these cases was the preoperative management and preparation of the patient. Emphasis will therefore be placed on the preoperative management and the effect of this on the immediate operative mortality.

Factors which enter into the prevention of such fistulas will not be mentioned, except to emphasize that a great part of the rationale of preoperative management of fistula is based on the knowledge that the disease is a manifestation of a long-standing debilitating process. Furthermore, most of the patients are not cooperative with medical treatment, as evidenced by the fact that in most of the cases reported here the duodenal ulcer, then the gastrojejunal lesion and, finally, the gastrocolic fistula, developed while the patient was receiving medical care. It is apparent also that the inanition and avitaminosis resulting from such lesions may be productive of postoperative peritonitis, tetany and pneumonia.

DATA ON PATIENTS

None of the 49 patients of this series were women. All patients had undergone gastroenterostomy for duodenal ulcer. In 40 cases posterior gastroenterostomy alone was the primary procedure. In 8 cases, previous acute perforation of a duodenal ulcer had occurred; the opening was closed, and posterior gastroenterostomy was performed then or later. The duodenal ulcer of 1 patient had been excised and posterior gastroenterostomy performed; the usual symptoms of duodenal ulcer had occurred. Of the 49 patients, only 7 had cooperated in their medical treatment; the rest had been listed as poorly cooperative or non-cooperative.

In 14 cases in this series, further operations had been performed on the stomach after the initial gastrojejunostomy and prior to the formation of the fistula. These operations, which were usually made necessary by the formation of an anastomotic ulcer, consisted preponderantly of

7. Walters, W., and Clagett, O. T.: Gastrojejunocolic Ulcer and Fistula, *Ann. J. Surg.* 46:94-102 (Oct.) 1939.

some type of plastic or short-circuiting procedure. The operations were almost always futile, unless some type of gastric resection was performed. Even then the fistula ultimately formed. Whether early gastric resection would have forestalled the final penetrating ulcer cannot be said definitely. One patient had undergone four such intervening operations. Two years after the initial gastrojejunostomy, an enteroanastomosis for correction of a malfunctioning stoma was carried out. A year later an exclusion operation of the Devine type was performed in an attempt to control the anastomotic ulcer. In five months the gastrojejunal ulcer was excised without changing the continuity of the gastrointestinal tract. Nine years later a Billroth I operation of the von Haberer type was performed. Two patients required three such intervening operations; 4 had two, and the remaining 7 patients had one operation between the gastroenterostomy and the final operation.

The necessity for repairing the gastrojejunocolic fistula occurred on an average five years after the initial gastroenterostomy, but in 1 case twenty-nine years had passed before symptoms of fistula developed, and in another case barely a year had passed before a well developed gastrojejunocolic fistula was demonstrated. The youngest patient to have a fistula was 27 years of age. He had been aware of the presence of a duodenal ulcer since the age of 15 and had had symptoms of gastrocolic fistula for four months prior to registration at the clinic. Gastroenterostomy had been performed when he was 18 years of age, and he had had two subsequent operations for ulcer at the anastomosis. The oldest patient was 65 years of age when repair of the fistula was attempted. The average age of the patients was about 46 years.

SYMPTOMS

The symptoms heralding the development of gastrojejunocolic fistula usually are easily distinguished. The history and the aspect of the patient are rather typical. The story is one of long-standing recurrent distress from the ulcer, for which gastroenterostomy first had been performed and occasionally had been followed by other operative attempts to control the continued distress caused by the anastomotic ulcer. A gastrojejunocolic fistula cannot develop unless the anastomotic ulcer is present first. The severe pain of anastomotic ulcer and a shift of pain from the epigastrium to the umbilical region and left side of the epigastrium occur. In the absence of a definite fistula, symptoms of colonic irritation are suggestive of an impending break into the colon. A roentgen diagnosis of gastrojejunal ulcer prior to establishment of a communication between the stomach and the colon was made in a large percentage of cases in this series. In about 30 per cent of the cases the patient had had hemorrhages of various degrees of severity from the anastomotic ulcer before development of the fistula.

With establishment of the fistula the pain usually ceases and diarrhea begins. The stools are usually watery and copious and finally contain large quantities of undigested food which has recently been ingested. Occasionally the patient has a ravenous appetite, but usually there is anorexia with marked loss of weight. Hemorrhage occurred after development of the fistula in 10 per cent of our cases; in 30 per cent of these it occurred before final establishment of the fistula. Frequently patients with gastrojejunal fistula complain of a bad taste in the mouth, and about 60 per cent of them will notice foul-smelling eructation. One patient belched while lighting a cigaret and was amazed to see a flare of flame. Fecal vomiting, which usually occurs late in the course of the disease, is found in 15 per cent of the cases. Dehydration, emaciation and nutritional edema may develop rapidly, depending on the size of the opening and the quality of the diet. If the symptoms are allowed to progress unchecked by reparative procedures, pellagra may develop. In a large percentage of cases avitaminotic manifestations of lesser degree will develop.

On admission to the hospital for preoperative preparation, only 13 of the 49 patients were in good condition; 8 more were in relatively good condition. Twenty-seven had edema of the limbs, the abdomen or the face in varying degrees; marked emaciation and loss of weight were the rule. Twenty patients showed some evidence of avitaminosis, and 9 had associated mental derangement, dermatitis and glossitis. One patient had definite carpopedal spasm. Serious anemia was present in only a few cases; in these cases hemorrhage had occurred.

DIAGNOSIS

The diagnosis of a well developed gastrojejunal fistula when the history and the aspect of the patient are kept in mind is not difficult. In about a fourth of the cases an inflammatory mass can be palpated in the epigastrium or just above the umbilicus. If roentgen studies are to be made, the method of choice includes a barium sulfate enema. In these 49 cases a well developed fistula was present, yet a positive roentgen diagnosis was made in only 13 of the 40 cases in which roentgenograms of the stomach were made. In 25 cases in this series roentgen examination of the colon was made after a barium sulfate enema had been given; the fistula was demonstrated in each instance.

The laboratory studies with the exception of the chemical findings of the blood and the values for serum protein were not remarkable. A slight hypochromic anemia was usually present. In cases in which repeated hemorrhage had occurred, rather serious anemia prevailed. The gastric acidity was slightly elevated in those cases in which intervening partial gastric resection had not been performed for gastrojejunal ulcer, but the total acidity was never more than 100 or the free hydrochloric acid ever more than 65 (Töpfer's method). The usual test meal

revealed a total acidity of about 50 and free hydrochloric acid of 35 to 40. In the cases in which gastric resection had been performed, the total acidity and free hydrochloric acid were markedly lowered. The total protein was determined in 17 cases; in 11 the value was less than 5 Gm. per hundred cubic centimeters of serum at the time of admission. The albumin-globulin ratio was disturbed to some extent in most of the cases. The level of vitamin C in the plasma was not determined in enough cases to warrant definite conclusions. However, the test was carried out in 7 cases. Normal values range from 0.9 to 1.5 mg. per hundred cubic centimeters of plasma; in only 1 of the 7 cases did the level of vitamin C fall within normal limits. In the remainder it varied from 0.49 to 0.8 mg. per hundred cubic centimeters.

PREOPERATIVE PREPARATION AND ITS EFFECT ON OPERATIVE MORTALITY

Preparing these patients thoroughly and adequately for the extensive operative procedures necessary to effect a cure presents a formidable problem. As can be seen, the clinician is dealing with a patient who is surviving with difficulty the ravages of inanition and whose reserve for reparative processes after operation is low. Furthermore, the chemical constituents of his blood are out of balance, and his courage and will to live are at low ebb because of the nature of his disease. The surgeon cannot assume the responsibility of an attempt at closure of the fistula until the patient has regained some measure of strength and reserve, and the grave risk attending surgical procedures on such patients is obvious.

In this series of 49 cases there were 18 postoperative deaths, a mortality rate of 36.7 per cent. As already pointed out, cases in which the surgeon noted an impending fistula and in which the mortality rate was greatly lower were not included. In order to determine to some degree the effect of preoperative preparation of the patients on the operative mortality rate, they were divided into three groups.

Group 1.—This group consisted of 13 patients (26.5 per cent of the series) who seemed in good condition on admission to the hospital. Seven were considered such good risks that operation was performed on them the day after admission. The chemical constituents of the blood, the serum protein and the results of routine blood studies were normal in 11 cases. None of the patients in this group showed clinical evidence of avitaminosis, but 5 had edema of either the ankles or the abdomen. Because of these findings, the hazards of the proposed operation were thought to be greatly less and meticulous preoperative preparation was thought unnecessary. Yet this group of patients in relatively good condition ultimately did far worse after operation than

another group who were so ill on admission that careful preparation was necessary before they could be subjected to operation.

The average stay in the hospital before operation was less than two and a half days. In no case was an attempt made to cleanse the colon with repeated enemas, to give vaccine intra-abdominally or to administer low residue or residue-free diets. Three of the patients were given fluids by the intravenous route before operation, usually a 5 per cent solution of dextrose in distilled water. No attempt was made to increase the body's store of vitamins. Eight of 13 patients died after operation (a mortality rate of 61.5 per cent). Nearly half (44.4 per cent) of the deaths in the entire series occurred in this small group.

Because of the high operative mortality rate in this small group of cases in which preoperative preparation was not given, it was interesting to study the effect of preoperative preparation on the mortality rate. This study was undertaken with groups 2 and 3 to determine if possible what method of preparation would give the patient the best chance of cure.

Group 2.—This group consisted of the remaining 36 patients, who were considered more thoroughly prepared for operation. Ten died (a mortality rate of 27.7 per cent). A little more than half (55.6 per cent) of the deaths in the entire series were in this group, yet the mortality rate (27.7 per cent) was definitely lower than that of the whole series (36.7 per cent).

The average preoperative stay in the hospital was seven and seven-tenths days. When chemical examination of the blood revealed abnormality, the patient was kept long enough to permit the amount of urea and chlorides and the carbon dioxide-combining power of the blood to return to normal. In the majority of cases vitamins, usually two capsules of halibut liver oil and six tablets of brewers' yeast daily, were given routinely. In 19 cases cleansing enemas were given night and morning for two or three days before operation, and low residue or residue-free diets were employed throughout the preoperative period. In 15 of the 19 cases, 0.5 to 1.0 cc. of vaccine was given intraperitoneally in addition to the regular preparation of the colon. The prothrombin time (Quick test) was normal in instances in which it was obtained. Vitamin K was not given to the patients in this group. Fluids, usually a 5 per cent solution of dextrose in a 0.9 per cent solution of sodium chloride, were given intravenously to 24 of these 36 patients.

Group 3.—This group consisted of 7 patients who also were included in group 2. These patients are grouped separately because their preoperative preparation was as thorough as possible, and only 1 postoperative death occurred. All 7 of these patients were in worse condition on admission than the average patient of the total series. All were greatly emaciated, and 6 had marked nutritional edema of the ankles

and the abdomen. One had rather serious pyelonephritis, and another had mild mental changes, which together with his avitaminotic state and dermatitis suggested pellagra. The chemical findings in the blood were not more abnormal than is usual in this type of case, but in 2 cases the values for the proteins were less than 5 Gm. per hundred cubic centimeters of serum. Determinations of vitamin C in the plasma were made in only 3 of these cases; the values were below normal in all 3. However, in these 7 cases there was only 1 death, and that occurred on the seventeenth day after operation and was caused by peritonitis. Perhaps the fact that each of the patients was in even worse than usual condition on admission led to more painstaking preparation for operation. A postoperative mortality rate of only 14.2 per cent after repair of gastrojejunocolic fistula performed in one stage in 7 such cases is remarkable.

The average preoperative stay in the hospital for these 7 patients was slightly more than nine days. They all received daily at least 2,000 cc. of a 5 per cent solution of dextrose in a 0.9 per cent solution of sodium chloride intravenously. Two received transfusions of 500 cc. of citrated blood. In each case the colon was prepared in the usual way; that is, cleansing enemas were given morning and night for two or three days before operation. In addition, all patients received vaccine intraperitoneally, low residue diets and massive doses of added preparations of vitamins daily, the exact amounts depending on the patient's needs. The usual routine for the daily administration of such vitamins included: (1) 100 to 200 mg. of ascorbic acid orally or 100 mg. intravenously; (2) 100 to 150 mg. of nicotinic acid orally or 50 to 100 mg. intravenously; (3) 15 to 30 mg. of thiamine hydrochloride orally or 5 to 15 mg. intravenously; (4) 30 drops of percomorph liver oil; (5) some form of vitamin D (halibut or cod liver oil in bulk or capsules); (6) six to twelve tablets of brewers' yeast daily. These amounts were varied according to the patient's needs.

From study of groups 2 and 3 it is clear that no single therapeutic measure will cause significant lowering of the operative mortality rate. Each patient must be studied and treated individually. Hard and fast rules of preoperative management cannot be given, although a logical rationale of preoperative management is suggested by this study.

SURGICAL CONSIDERATIONS

If a procedure of one stage is contemplated for the repair of a gastrojejunocolic fistula, some such method of preoperative management would seem wise. Preliminary jejunostomy is recommended by some surgeons and in their experience has given good results. Scrimger⁸

8. Scrimger, F. A. C.: A Technic for the Management of Gastrojejunal Ulcers With or Without Gastrocolic or Jejunocolic Fistula, *Ann. Surg.* **104**:594-600 (Oct.) 1936.

suggested a technic in which the edges of the gastric mucosa from the cuff of the anastomotic ulcer are sutured together over the fistula; a posterior Polya type of gastric resection is then carried out, utilizing portions of the jejunum distal to the fistula. In 5 cases reported, 1 death occurred. One patient in our series was subjected to preliminary jejunostomy but died thirteen days after the operation of perforation of a gastric ulcer and resulting peritonitis and uremia. Many other suggestions of technic have been advanced, occasioned no doubt by the high mortality rate attending the accepted types of repair. Allen³ has suggested resection of the colon, jejunum and stomach en masse by the Kerr aseptic technic of anastomosis for restoration of continuity of the gastrointestinal tract. Finsterer⁹ preferred to carry out the procedure in a single stage but recommended an operation in two stages if simple closure of the fistula could not be performed. Findlay¹⁰ recommended a multiple stage operation.

Perhaps one of the most encouraging suggestions is that of Pfeiffer,¹¹ who recommended preliminary loop colostomy in preparation for final repair of the fistula at a second stage. In this way the fecal current is diverted above the fistula, giving the inflammatory process at the site of the fistula time to heal and averting colonic contamination. The general condition of the patient can be improved greatly in this way in preparation for final repair of the fistula.

SUMMARY

A series of 49 cases in which patients were operated on at the Mayo Clinic from 1930 to 1939, inclusive, is reviewed from the standpoint of medical preoperative management. Of the 49 patients, 18 died after operation; the mortality rate was 36.7 per cent. Of 13 patients who received practically no preoperative preparation, 8 died; the mortality rate in this group, then, was 61.5 per cent. Of the remaining 36 patients, all of whom had fairly satisfactory preparation, 10 died—a mortality rate for this group of 27.7 per cent.

Only 1 of 7 patients, all of whom were in worse condition on admission than usual and who received careful and adequate preoperative treatment, died—a mortality rate of 14.2 per cent.

It is suggested the prohibitive mortality rate after reparative procedures performed in one stage for gastrojejunocolic fistula can be lowered materially by adequate preoperative management.

9. Finsterer, H.: Results of Repeated Operations upon the Stomach Especially for Gastrojejunal Ulcers, *Surg., Gynec. & Obst.* **68**:334-346 (Feb. 15) 1939.

10. Findlay, F. M.: Treatment of Gastrojejunocolic Fistula by Multiple Stage Operations, *Arch. Surg.* **32**:896-906 (May) 1936.

11. Pfeiffer, D. B., and Kent, E. M.: The Value of Preliminary Colostomy in the Correction of Gastrojejunocolic Fistula, *Ann. Surg.* **110**:659-668 (Oct.) 1939.

CONGENITAL DUODENAL OBSTRUCTION

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Acute intestinal obstruction is always such a serious illness that it demands prompt recognition and treatment to prevent a fatal termination. This is just as true when it occurs in infants as when it occurs in adults, with the further consideration that infants, being inarticulate, often are subjected to delay in diagnosis, and this results in their contributing more than their share to the high mortality rate.

When one is reminded that the first successful operation for the cure of duodenal obstruction in an infant was reported as recently as 1916,¹ there seems some justification for the past failures of those responsible for the medical care of infants to recognize the condition. That the point in pediatrics has been reached where the disease, whether acquired or congenital, is more promptly recognized is attested by the increasing number of cases reported. There has been an unjustifiable tendency to consider gastric and intestinal disorders of the baby as errors of digestion or nutrition, but this diagnostic complacency is rapidly being displaced by scientific and common sense observation on the part of physicians.

Congenital duodenal obstruction is not a common condition, but its frightful mortality rate gives it an importance among the diseases of infancy and childhood second to no other illness.

A brief résumé of the mechanical factors involved is a good background for the consideration of the symptoms and treatment. In the second and third month of fetal life,² the entire gastrointestinal tract is a simple rod of epithelium and mesoderm, with practically no lumen. The cephalic end dilates into a rudimentary stomach, the midportion

1. Ernst, N. P.: A Case of Congenital Atresia of the Duodenum Treated Successfully by Operation, *Brit. M. J.* 1:644 (May 6) 1916.

2. Callander, C. L.: *Surgical Anatomy*, Philadelphia, W. B. Saunders Company, 1933. Arey, L. B.: *Developmental Anatomy*, ed. 3, *ibid.*, 1934.

grows in length and assumes the form of superimposed coils, while the caudal extremity dilates slightly to become eventually the sigmoid flexure and the rectum. All of this embryonic tract lies on the left side of a shallow abdomen. The small bowel increases in length and projects itself, for lack of space, into and through the umbilicus into the cord so that, in reality, a hernia is created. For some reason unknown to those best qualified to state, the small bowel is retracted soon after and

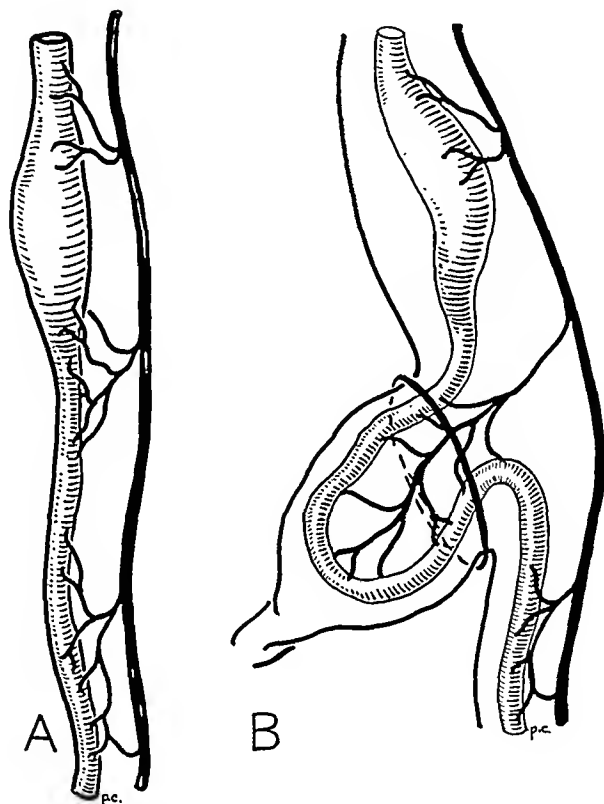


Fig. 1.—*A*, primitive gastrointestinal tract. *B*, elongation of the small intestine and its projection through the umbilical canal.

returns to the left side of the abdomen. An unyielding short mesentery is one explanation of the out and in mechanism. In the upper left quadrant of the abdomen, in the region of the spleen the large bowel joins with the small intestine and extends directly downward to become later the descending colon, sigmoid flexure and rectum. About the third month, the colon grows in length, pushing the cecum, which has been in the region of the spleen, over into the lower right quadrant of the abdomen, where it becomes firmly attached. This is known as the rota-

tion of the colon. In this movement, the leaf of the mesentery and the superior mesenteric artery are involved and apparently angulated to some extent. The colon continues to grow two of its fixed points, the

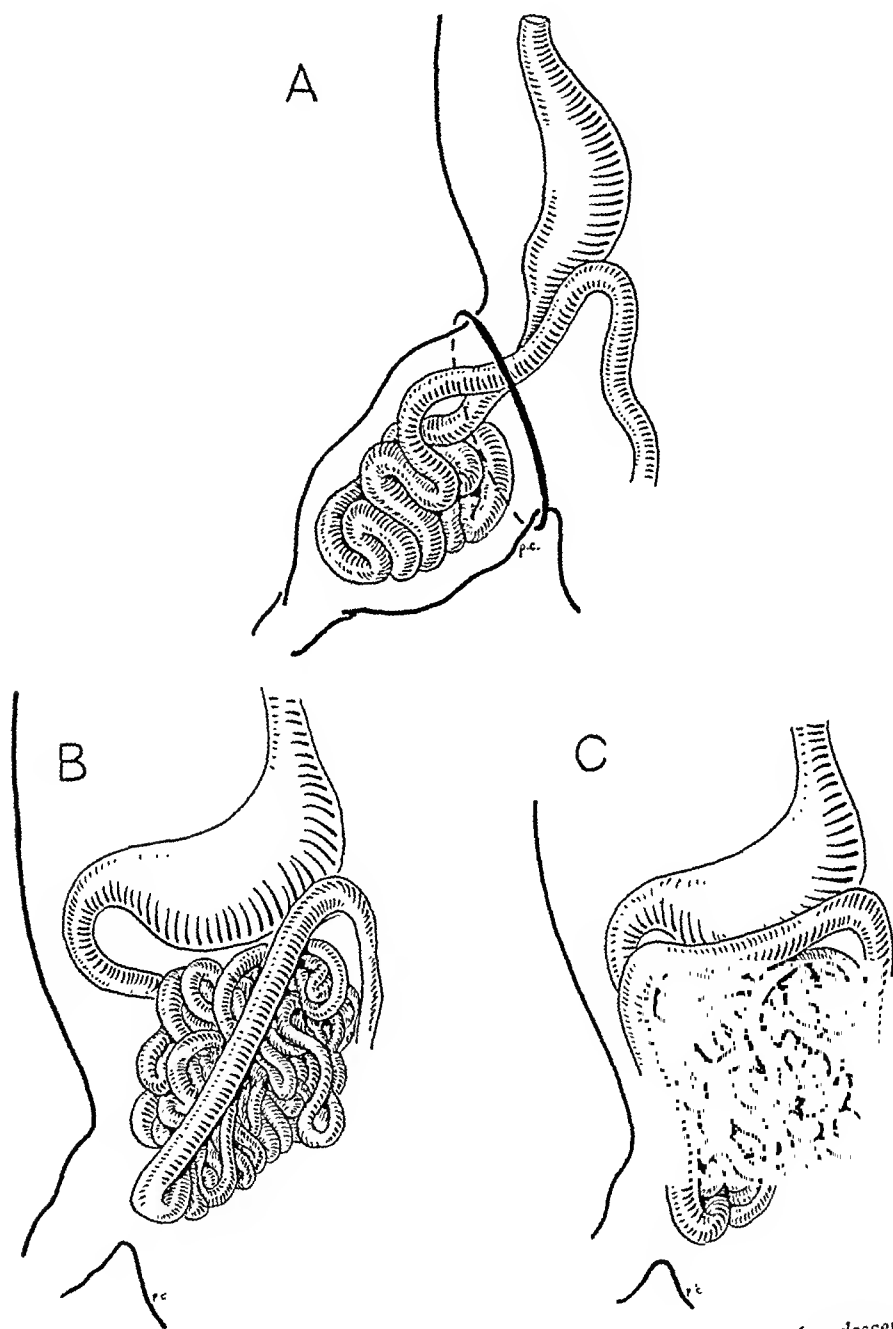


Fig. 2.—*A*, the small intestine greatly increases its length. *B*, the colon descends and rotates. *C*, the colon elongates to form the ascending and transverse colon.

lower right and the upper left quadrant of the abdomen, and the additional length goes into the space formerly occupied by the liver. The liver, which has been a relatively large organ up to this time, either

recedes beneath the ribs or actually diminishes in size. The portion of the large bowel filling this space becomes the ascending colon, hepatic flexure and transverse colon and covers the duodenum and proximal part of the jejunum. It is in this development and rotation that deviation from the normal manner results in angulation or compression of the duodenum. In all but 1 of every 20,000 cases the adjustment is perfect

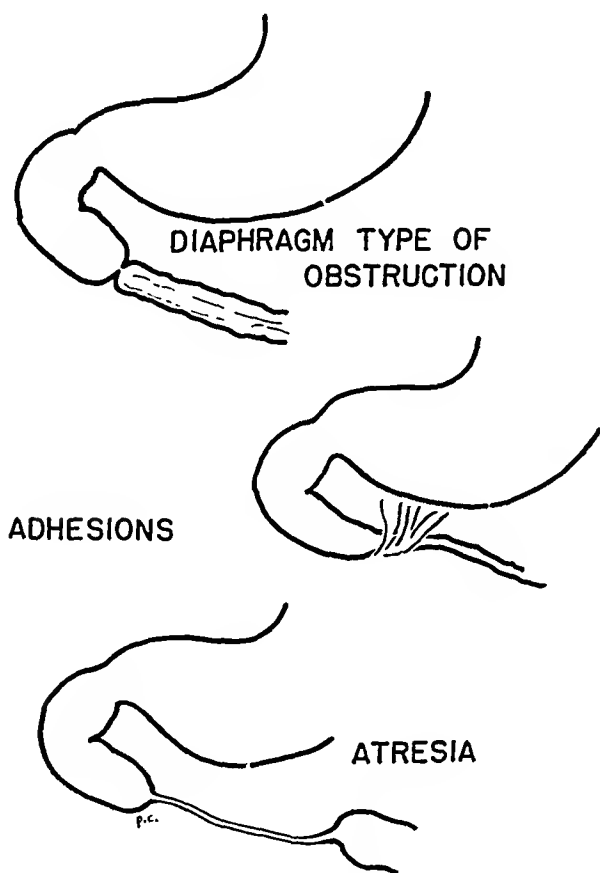


Fig. 3.—The types of duodenal obstruction.

and the function of the intestine is uninterrupted. The 1 case is that of duodenal obstruction.

Other forms of obstruction are recognized anatomically. An unusual type is one in which a diaphragm or septum develops within the duodenum; this is known as an intrinsic obstruction. The most common obstruction is the atresia or failure of the bowel to develop a lumen, leaving the intestine merely a stringlike continuation of the duodenum. This may be and often is multiple. It seems futile to seek an explana-

tion for these errors and defects in development; it is sufficient today to recognize their presence.

In most cases, the obstruction dates from birth, and, except in those rare ones in which an incomplete diaphragm is present in the duodenum, the onset of symptoms is prompt and continuous. Vomiting stands out as the most conspicuous and important symptom and is therefore entitled to the most careful consideration. It appears shortly after birth and continues until it is relieved by appropriate measures or until the patient

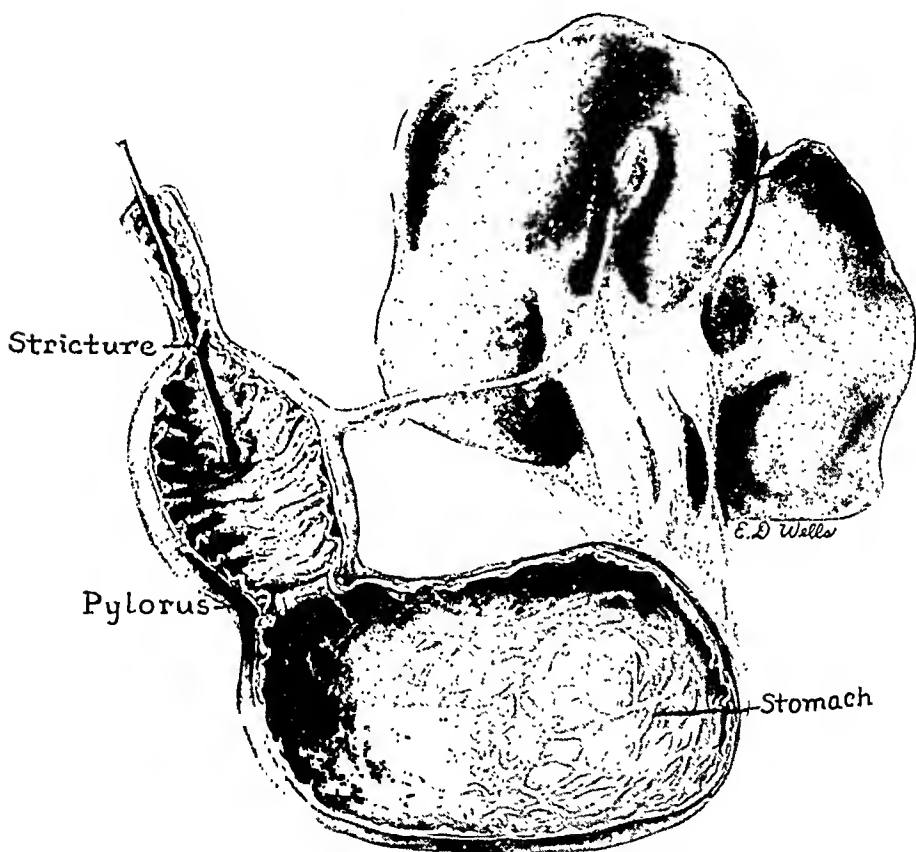


Fig. 4.—Specimen showing the intrinsic or diaphragmatic type of obstruction.

succumbs. It does not follow feeding as promptly as in pyloric stenosis, and in most instances bile and duodenal contents (readily recognizable by odor and color) are present.

The stomach may be dilated, and the physical examination should demonstrate this; the lower part of the abdomen, however, will be flat. There should be no hesitation in using a thin feeding of barium sulfate to outline the stomach and duodenum and thus localize the obstruction. As a rule, the stools consist chiefly of meconium.

It has been pointed out that if the lesion in the duodenum is proximal to the opening of the common bile duct, bile will not appear in the

vomitus, and a picture identical with pyloric stenosis presents itself. A diagnosis of this condition in itself is no great commission of error if the obstruction is recognized and treated surgically when the differentiation is made at the time of operation. Suffice it to state that other symptoms of intestinal obstruction are present, and the recognition of the condition should not be insurmountable. Too much emphasis cannot be placed on the necessity of furnishing food and fluid to the dehydrated and starved victims of obstruction prior and subsequent to surgical measures.

In a reasonable search of the literature, we have found no accurate study made of comparative blood counts and blood analyses in these cases, but we have no doubt that they run parallel to those in the cases of adults. In the latter, moderate leukocytosis, decrease in chlorides and hypoproteinemia are the major changes. This should prove a valuable and interesting study.

It would seem that the urgency of these cases demands prompt diagnosis and surgical treatment. If there is any medical situation in which time is an element in the treatment, it must be acute intestinal obstruction in infants. In too many cases operation is postponed until no hope of a successful outcome can be entertained.

The diagnosis in most cases can be made on the basis of the short period after birth in which vomiting occurs, together with the persistence and type of the vomiting and the nature of the material ejected. Roentgen examination is of positive value and should be utilized more frequently. If the physician expects to delay and fortify the patient by intravenous injection of solutions or of blood, he is doomed to disappointment. The catalytic elements in the disease outweigh the constructive assistance furnished by parenterally injected solutions. McIntosh and Donovan³ observed:

Some of the authors writing on this subject have laid emphasis on the part played by volvulus in producing the symptoms of obstruction, while others have stressed the kinking and compression of the duodenum by congenital peritoneal bands and the constricting effect of other malformations of the mesentery. Our series includes examples of all of these types, and we wish to point out that preoperative differentiation among them is always difficult and often impossible.

The treatment is surgical. The intravenous injection of solutions prior to the operation is recommended, but temporizing with the hope of raising the resistance of the patient is not justified in the light of experience. Plasma is the logical substitute for blood and should be used freely.

There is no necessity for detailing the steps of the operation. The operator should always bear in mind that the patient offers a poor

3. McIntosh, R. R., and Donovan, E. J.: Disturbances of Rotation of the Intestinal Tract, *Am. J. Dis. Child.* 57:116-166 (Jan.) 1939.

risk, that no time must be wasted, that one of several operations is permissible and that the tissues involved are often of transparent thinness and permit only the gentlest manipulation. With these facts before him, he should see to it that the stomach has been lavaged, that the child is well protected by warm coverings, that the induction of anesthesia is in capable hands and that the after-care, particularly the feeding, is supervised by one of wide experience. The absence of any one of the foregoing essentials may lead to an unnecessary fatality.

The types of operations in general use are as follows: liberating adhesions, opening the bowel, dividing the diaphragm and closing the opening in the bowel, gastroenterostomy, duodenojejunostomy. Ladd, who has had wide experience and has reported more personal cases than any one else, prefers an operation that bears his name for the extrinsic obstructions. All types of operations are difficult and attended with considerable mortality. It will require further study of the patients who have recovered, after the lapse of several years, as well as of those who have succumbed, to propose a basis for a standardized operation for each type of obstruction. No type of enterostomy has been successful, and this procedure should be eliminated as a palliative or curative measure.

Up to 1932, Ladd could find but 10 cases in which there had been successful operation, and of these he had 7. To illustrate the celerity with which the disease has been recognized, in 1937 Ladd⁴ reported 28 additional cases in the Childrens' Hospital in Boston. His great experience gives weight to his statements, and we quote almost verbatim from a description of his operation. The procedure consists of a long incision of the right rectus muscle through which the entire small intestine is delivered and unrotated if a volvulus is present. In one or two instances this gave relief at once but later proved insufficient. The next step consists in mobilizing the ascending cecum and the proximal half of the transverse colon until the duodenum is completely visible. If there are any folds of peritoneum or bands which impinge on the duodenum and constrict it, they are severed, care being taken to protect the superior mesenteric artery. Ladd had 19 recoveries in 23 cases, with a satisfactory follow-up record.

We have operated on 4 such patients. The first we lost by failure to recognize the nature of the obstruction, which was of the intrinsic type. The remaining 3 had obstruction of the extrinsic or adhesion type and were treated by gastroenterostomy. We probably did not employ the best type of operation, but in 2 of the cases we felt that the condition was so critical that evisceration and mobilizing the colon would

4. Ladd, W. E.: Congenital Duodenal Obstruction, *Surgery* 1:878-885 (June) 1937.

have been more than the patient could survive. The 3 patients have gained weight and thrived. They will furnish subjects for an absorbing study in years to come. We are of the opinion that Ladd's operation is rational and the one of choice, but in exceptional circumstances another operation meets the situation quite as well.

SUMMARY

Congenital duodenal obstruction is an uncommon condition and highly fatal in the absence of prompt diagnosis and treatment. Vomiting is an early and persistent symptom and should arouse suspicion of intestinal obstruction in the newborn. Bile is usually present in the vomitus. While the exact nature and location of the obstruction cannot always be known before operation, a diagnosis of intestinal obstruction is possible early in the majority of cases. The taking of a "scout" roentgen film or of a film after the oral administration of barium sulfate is both safe and desirable. Operation is the only treatment which offers a hope of cure but must be employed early, preferably by one with experience in pediatric surgery.

Dehydration and shock should be combated by parenteral administration of fluids, of which plasma is the most valuable.

The preoperative and the postoperative care rank equally high in importance with the operation. Our preference is for general anesthesia induced by administration of ether by the drop method. Many prefer local anesthesia. All types of anesthetization demand the services of a competent anesthetist.

PROGRESS IN ORTHOPEDIC SURGERY FOR 1940

A REVIEW PREPARED BY AN EDITORIAL BOARD OF THE AMERICAN
ACADEMY OF ORTHOPAEDIC SURGEONS

(Continued from page 734)

XIV. CONDITIONS INVOLVING HIP JOINT

Anatomy and Physiology.—The use of multiple drill holes to revascularize the head of the femur has now become common. Compere, Garrison and Fahey⁴²⁸ have investigated experimentally the possibility of permanent injury to the capital and greater trochanteric epiphyses by multiple drilling. One or both of the two major growth centers of the proximal end of one femur in each of 27 goats 6 weeks old were subjected to operative trauma by curettage or multiple drilling. After maturity had been reached, nineteen months later, the animals were killed, necropsy was performed, and the femurs were removed for study, measurement and roentgen examination. The authors conclude that surgical trauma to the greater trochanteric epiphyses by drilling or curettage causes arrest of growth with resulting deformity and shortening of the greater trochanter and associated coxa vara. Similar surgical trauma to the epiphysial cartilage plate of the head of the femur usually results in arrest of growth, which produces a shortening of the neck of the femur, an irregular contour of the head of the femur, coxa vara and a functional shortening of the shaft of the femur. The authors conclude from their experimental work that drilling the neck of the femur of a young child to hasten revascularization of the head, as in cases of Legg-Perthes disease, is a questionable procedure.

Mouriquand, Dauvergne and Edel⁴²⁹ report further results of prolonged experimental deficiency of vitamin C in dogs. They have been able to demonstrate that deficiency of vitamin C of sufficient duration produces decalcification of the bones, mostly at the extremities, calcium deposits and formation of new bone in the subperiosteal regions and in the soft tissues in the neighborhood of joints. They have found that the effect in the head of the femur is so pronounced that it becomes

428. Compere, E. L.; Garrison, M., and Fahey, J. J.: Deformities of Femur Resulting from Arrestment of Growth of Capital and Greater Trochanteric Epiphyses, *J. Bone & Joint Surg.* **22**:909-915 (Oct.) 1940.

429. Mouriquand, G.; Dauvergne, M., and Edel, V.: Irreversible Decalcification of Femoral Neck in Chronic Vitamin C Deficiency, *Presse méd.* **48**:268-269 (March 12) 1940.

completely decalcified. While the outline of the head and the neck of the femur disappears, the acetabular cavity becomes filled with bony proliferations. Similar results, although less marked, are produced by a diet only partially deficient in vitamin C (e. g. one containing 0.5 mg. of ascorbic acid per day). This curious syndrome, once produced, is irreversible, and recalcification of the head and neck of the femur could not be effected either by supplementing the diet with as much as 50 mg. of ascorbic acid per day for as long as one hundred and eleven consecutive days or by the administration of massive doses of vitamin D. The authors suggest that the physician bear their experimental findings in mind when confronted with decalcification of obscure origin localized in the head and the neck of the femur of a child.

Bifurcation Operation on the Hip.—Milch⁴³⁰ advocates the bifurcation operation because it is a simple procedure which can be quickly performed and which gives a stable hip and relieves pain. The objection to this operation is that it produces knock knee and limitation of motion. Milch feels that the knock knee deformity is not of great significance.

He has observed a tendency in children for the original bifurcation to disappear and for the spike of bone which constitutes the upper end of the distal fragment to be absorbed. In adults this change in the configuration of the bone does not take place. Disability occurs in cases in which the anomaly is unilateral; it becomes well pronounced in many cases in which the bifurcation operation is performed on both sides. This disability is associated with limitation of abduction, rotations and flexion. The patient has a distinct waddle in walking because he cannot bring his legs together in the normal fashion. Milch notes in children that as the spike disappears these symptoms are gradually improved. He argues that this is an indication for the removal of the spike. In adults with pronounced symptoms there were marked increase in the range of motion of the joint and absence of pain after the spike was removed. He believes that the spike is not essential to successful osteotomy but that on the contrary it is the cause of the undesirable effects found almost routinely after a typical bifurcation operation.

Slipped Epiphyses.—Ghormley and Fairchild⁴³¹ in a general discussion of slipped epiphysis of the femur emphasize that the term "slipped epiphysis" is a misnomer, because the epiphysis retains its position in the acetabulum while the neck and shaft of the femur rotate externally and ride upward. They point out that Milch proposed the term "epiphysal coxa anteverta" and that the term "epiphysiolysis" is apt but will probably not supersede the commoner expression "slipped epiphysis."

430. Milch, H.: Bifurcation Operation, *Surgery* 8:686-698 (Oct.) 1940.

431. Ghormley, R. K., and Fairchild, R. D.: Diagnosis and Treatment of Slipped Epiphyses, *J. A. M. A.* 114:229-235 (Jan. 20) 1940.

Pitzen⁴³² distinguishes three types of coxa vara: the congenital, the rachitic and the adolescent or static. Congenital coxa vara is due in his opinion to a disturbance of endochondral ossification, which is shown in roentgenograms as a rarefaction in or lateral to the epiphysial line. [ED. NOTE: However, he presents no evidence for this opinion.] Coxa vara in adolescent patients he ascribes to a softening process in the metaphysis of the neck of the femur which allows the epiphysis to slip downward and backward, a shift demonstrable in a lateral roentgenogram. He describes the histologic characteristics of osteomalacia localized in the metaphysis of the neck which he concludes is associated with disturbance of the internal secretions of the gonads and the hypophysis. [ED. NOTE: No detailed evidence for these conclusions is presented, and the histologic observations, if corroborated, are open to another interpretation, namely, that the rarefaction is secondary to the slipping.]

Waldenström⁴³³ also feels that the condition is fundamentally due to an endocrine disturbance of the adiposogenital type. He believes that this disturbance may be transitory. Waldenström judges the length of time during which slipping may occur by determining the maximum time between the onsets of slipping on one side and the other when the anomaly is bilateral. In his series of cases the interval has been one and one-half years. However, it is becoming increasingly apparent from the literature that by no means all, in fact only the minority, of the cases are of the so-called endocrine type. This is brought out by Ghormley and Fairchild, who, after reviewing the trauma, infection and endocrine disturbance hypotheses of causation, conclude that trauma together with the mechanical disadvantage of the epiphysial plate is probably the usual, if not the sole, cause of displacement. The mechanical disadvantage is greater during adolescence because of the relatively increased weight of the body and the obliquity of the epiphysial line. With this in mind they discuss the types of patients and show that in their series 18 patients were normal in weight and 26 were obese or of unusually large build. However, of the latter 26, 14 were constitutionally obese and for only 12 was there sufficient evidence to suggest some endocrine syndrome.

To test Brailsford's⁴³⁴ hypothesis that slipping of the epiphysis is due to renal rickets, Waldenström carefully examined 7 consecutive patients by clinical and laboratory means for evidence of renal rickets.

432. Pitzen, P.: Coxa Vara: Its Causes and Treatment, *Med. Klin.* **36**:344-347 (March 29) 1940.

433. Waldenström, H.: Slipping of Upper Femoral Epiphysis, *Surg., Gynec. & Obst.* **71**:198-210 (Aug.) 1940.

434. Brailsford, J. F.: *The Radiology of Bones and Joints*, ed. 2, Baltimore, William Wood & Company, 1935.

Finding none, the author concludes that renal rickets is at most a rare cause of epiphysiolysis.

All these authors point out that any adolescent patient complaining of slight pain or limp should be regarded as possibly having a slipped epiphysis. The importance of a careful examination of an adolescent patient complaining of pain in the hip is emphasized. They show that the early signs of slipped epiphysis may be minimal and that there is only a slight limitation of internal rotation as compared with the rotation on the normal side. Roentgen examination should therefore include the sound side. Anteroposterior and lateral views are of equal importance.

Waldenström insists that roentgenograms should always be taken simultaneously, in the same relative position and at the same distance. The lateral view is taken with the hips flexed and abducted. This view he finds most helpful, and he says it should never be neglected. The significant roentgenographic appearances are three: The epiphysial hook is down; the metaphysial edge is up, and there is a broader epiphysial line.

Ghormley and Fairchild indicate the general dissatisfaction with the results of treatment. They state that all authors agree that the various stages of the condition require different methods of treatment and that few advocate one method to the exclusion of others.

They divide their treatment of the various stages as follows:

1. In the early slipping stage conservative treatment is advocated with discontinuance of weight bearing by crutches or a walking caliper splint until union of the epiphysis occurs.

2. (a) In the stage of gradual slipping the epiphysis is not completely separated and cannot be reduced by manipulation without injury; open operation with osteotomy of the neck of the femur is advocated as the treatment of choice.

- (b) In the stage of acute slipping superimposed on a gradual slipping or a preslipping stage a manipulative closed reduction is recommended if it is certain that the epiphysis is completely loose; if doubt exists, open reduction should be done.

3. In the stage of complete slipping of long standing treatment by open reduction or cervical osteotomy is recommended if the epiphysis is fused. They believe adults are best treated by arthrodesis if pain is pronounced or by acetabuloplasty if motion is to be preserved.

Pitzen considers nonoperative and operative methods. The former consist of traction, of freedom from weight bearing enforced by use of a plaster cast or an apparatus and maintained until fusion of the epiphysial line occurs and of reduction by manipulation in cases of recent slipping. Traction is used for young children, patients with rickets and some patients with recent epiphysiolysis. The reduction by manipulation is

were good in 2 cases, fair in 1 and poor in 1. Of the patients who were in the preslipping or early slipping stage, regardless of the type of treatment, all but 1 showed a good or fair result. The usual treatment was conservative. In 1 case, however, there was progress to a complete slip.

Blood Supply of the Hip.—An adequate blood supply to the head and neck of the femur is now assuming great significance because of the frequency with which aseptic necrosis is encountered in fractures and other lesions. Pollock⁴³⁹ has restudied the sources of blood supply by arteriography and divides the vessels as follows: (1) the diaphysial group, which springs from the nutrient artery of the femoral shaft; (2) the periosteal group; (3) epiphysial group, which derives from the circumflex artery; (4) the arterial group of the ligamentum teres femoris. Interference with any one source will result in disturbance of bone metabolism proportionate to the importance of the supply affected. Pollock believes that interruption of all four sources will be followed by necrosis of the entire head of the femur. He examined microscopically sections made from 23 heads of femurs in which there was no vascular supply except that carried by the ligamentum teres femoris or by adhesions. He found considerable areas of new bone formation in 22 of the specimens. In 1 there was no formation of new bone, and in this specimen he was able to demonstrate a complete lack of blood supply.

Coxa Plana.—The articles which have appeared on coxa plana or juvenile osteochondritis of the hip (Calvé-Legg-Perthes disease) show a definite tendency toward agreement with regard to treatment and prognosis. The etiology and roentgen pathology are still subjects on which various authors disagree.

Piergrossi⁴⁴⁰ and Lehmann⁴⁴¹ state that coxa plana is probably due to primary aseptic necrosis of the head of the femur with similar foci occurring simultaneously in the neck and in the acetabulum and that all the lesions are due to a common cause. Gill,⁴⁴² on the other hand, feels that the original site of necrosis is in the metaphysis. "The degenerative changes which occur in the head are also of the nature of aseptic necrosis, and are due to cutting off the blood supply through the metaphysis and the epiphyseal plate." [ED. NOTE: Vessels traversing the epiphysial

439. Pollock, G. A.: Changes Associated with Interference with Blood Supply of Head of Femur, *Mil. Surgeon* 86:254-255 (March) 1940.

440. Piergrossi, A.: Lesions of the Femoral Neck in Infantile Osteochondritis of Hip, *Radiol. med.* 27:81-108 (Feb.) 1940.

441. Lehmann, J. C.: The Progress of Epiphyseal Necrosis in Roentgenograms, with a Contribution to the Early Diagnosis of Perthe's Disease, *Deutsche Ztschr. f. Chir.* 253:132-144, 1940.

442. Gill, A. B.: Legg-Perthes Disease of Hip: Its Early Roentgenographic Manifestations and Its Cyclical Course, *J. Bone & Joint Surg.* 22:1013-1047 (Oct.) 1940.

plate have never been described.] This view is supported by Gill's observation that an area of rarefaction may be seen in the metaphysis preceding an epiphysal focus which later appears directly overlying it. Piergrossi points out that the metaphysal lesions may exist without concomitant changes in the epiphysis, leading to infantile coxa vara as described by Bertolotti.

Pathologic data are scarce. Pike⁴⁴³ studied a specimen removed at autopsy from the body of a 5 year old boy who died of a diaphragmatic hernia after an automobile accident. Although the child had complained of no symptoms referable to the hip, a roentgen examination of the pelvis shortly after the accident revealed flattening and segmentation of the epiphysis, broadening of the neck of the femur and thickening and widening of the joint space. At the time of death, seventy-two days later, the head and the neck of the femur were removed for study. Grossly, fragmentation of the epiphysis with areas of necrosis as well as zones suggestive of a degenerative change in the metaphysis was noted. One section was examined microscopically; this showed

considerable necrosis proximal to the epiphyseal line with considerable debris. No inflammatory reaction, however, is evident. There is some increased fibrosis and some round cell infiltration near the epiphyseal cartilage. The cartilage shows no actual change. Distal to the epiphyseal line, there is a partial necrosis of bone. The picture is of degeneration without particular inflammatory infiltration. There are areas of apparently dead bone. The marrow spaces are devoid of blood cells. Other areas show fairly normal cellular bone development with regard to cellular nuclei.

Pike states that these changes correspond to those seen by previous authors; he plans further study of the specimen.

Gill emphasizes the importance of early diagnosis and states that the disappearance of slight pain, muscle spasm and limitation of motion after a few days' rest in bed is deceiving. He also states that a firm slight thickening of the hip can almost always be felt by careful palpation.

Two aids in early roentgen diagnosis are described. Lehmann states that if immediate immobilization is carried out once the diagnosis is suspected, the atrophy of disuse in the pelvis and the femurs which ensues will not involve the aseptically necrotic epiphysis, which will present a striking contrast during the succeeding months. Gill finds that slight overexposure of the roentgenograms increases the facility with which the small metaphysal foci may be visualized.

The well known sequence of onset, degeneration and regeneration are described by Pike, Piergrossi and Gill. Piergrossi finds that cystic formations, zones of osseous condensation and shortening and thickening of the neck are the result of the metaphysal lesions and of the

443. Pike, M. M.: Legg-Perthes Disease with Particular Regard to Treatment, Connecticut M. J. 4:5-11 (Jan.) 1940.

concurrent changes in the periosteum of the neck and in the epiphysal cartilage. These authors agree that the major deformities consisting of flattening of the head of the femur, bowing of the neck and deformation of the acetabulum are the direct result of weight-bearing stresses during the course of the disease and emphasize the necessity for continuous freedom from weight bearing from first suspicion of the disease until the process is completed. This usually requires from two to three years. Pike points out that apparatus is necessary because children in the age group affected by the disease do not lie quietly in bed unless they are forcibly constrained. He advises the use of Buck's extension until pain and muscle spasm are alleviated and then the application of the Wu double hip splint. Other authors use continuous traction extension or immobilization in a plaster of paris cast. Walking calipers and other ambulatory braces are condemned because they allow minor degrees of weight bearing, which may be detrimental.

Ghormley and Fairchild emphasize the need for adequate treatment of osteochondritis and other conditions involving the hip in children because 22 per cent of a series of 154 adult patients seen at the Mayo Clinic had osteoarthritis as a late sequela of a disorder of the hip in childhood.

Gill presents 12 cases, and Pike reports 10, with serial roentgenograms for most of them. Excellent results, evidenced both by clinical and by roentgen examinations, have been obtained by early treatment of the disease in cases in which there was little original deformity of the head of the femur. The patients were restrained from all weight bearing. The normal contour of the head of the femur and the acetabulum was almost completely restored. In cases in which the disease has reached a later stage with marked deformity and fragmentation, but in which it is still in the phase of degeneration, remarkable reformation of the contour of the hip has been achieved by a similar regimen. Lehmann illustrates the result obtained by early and continuous treatment by a series of roentgenograms of a patient with bilateral Legg-Perthes disease. The patient was seen late in the course of the disease in one hip. Healing eventually occurred with marked flattening of the epiphyses. At this time symptoms appeared in the opposite hip, and immobilization in a plaster of paris cast was begun at once. Healing occurred with complete regeneration without deformity.

Ischiopubic Osteochondrosis.—Inclán⁴⁴⁴ reports 3 cases of ischiopubic osteochondrosis. It is characterized by pain, limp and limitation of motion of the hip joint, usually after trauma. Differential diagnosis may be difficult. Carefully focused roentgenograms show rounded

444. Inclán, A.: Osteochondrosis of Ischio-Pubic Branch of Hip Bone: Cases, Bol. Soc. cubana de pediat. 12:223-234 (June) 1940.

enlargement of the ischiopubic epiphysial zone with change in the density of the trabeculation.

The ischiopubic epiphysis closes between the age of 7 and 9 and not 10 and 12 as ordinarily stated. The time of closure may be delayed in hips with pathologic conditions. Rest in bed for several weeks is usually sufficient to relieve the symptoms. A definite cure follows closure of the epiphysial line.

Osteochondritis Dissecans.—King (D.) and Richards⁴¹⁵ review 26 cases of osteochondritis dissecans of the hip joint reported in the literature and add 2 of their own. The disease is a separate entity and may be diagnosed by the characteristic roentgen appearance. In doubtful cases diagnosis is possible only at the time of operation. The typical location of the sequestrum is on the superolateral aspect of the articular surface of the head of the femur above the ligamentum teres femoris. Clinically the disease is to be considered as a possibility in every young adult with a history of chronic pain in the hip, with a limp or with limitation of motion.

Surgical intervention with ablation of the osteochondritic focus gives definite symptomatic relief and offers the possibility of a permanent cure. The head must be dislocated from the acetabulum for proper visualization and removal of the focus. Because of the possible untoward sequelae which may follow this procedure, operation should be undertaken only after careful consideration.

Osteoarthritis of the Hip Joint.—In the treatment of this common ailment, the surgeon has a choice of a variety of methods, any one of which may possess merit in properly selected cases. Henderson⁴¹⁶ reports on the results secured in the treatment of a series of 77 patients at the Mayo Clinic from January 1926 to December 1937.

Manipulation was performed with the patient under anesthesia in 11 cases. Late results were known in 9, and in 4 of these improvement had been obtained. Drilling of the head and the neck of the femur was done in 28 cases. Twenty-five patients replied to follow-up inquiry. Nine reported improvement, and 4 were markedly relieved. Cheilotomy was done in 4 cases without removal of the proliferations about the acetabulum. Henderson considered this a useless operative procedure. Cheilotomy of the head of the femur and of the acetabulum was performed in 6 cases with definite benefit in 3. Cheilotomy and bone drilling were done in 3 cases. One patient continued to have pain; 1 was improving steadily, and 1 could not be followed. Acetabuloplasty

445. King, D., and Richards, V.: Osteochondritis Dissecans of Hip, J. Bone & Joint Surg. 22:327-348 (April) 1940.

446. Henderson, M. S., and Pollock, S. A.: Surgical Treatment of Osteoarthritis of Hip Joint, J. Bone & Joint Surg 22:923-931 (Oct.) 1940.

was used in 5 cases; 4 patients were slightly or moderately improved. In the 12 cases in which the Whitman reconstruction operation was employed, 6 patients were improved. Arthrodesis was done in 6 cases; 5 patients were followed; all had stable, painless hips.

Henderson concludes that the best results were obtained by arthrodesis, though union was slow, requiring six to nine months. Drilling combined with manipulation gave good results in many cases. Acetabuloplasty and extensive cheilotomy gave excellent results in some.

King (T.) reports the results secured with subtrochanteric osteotomy in 26 cases. Pain was completely relieved for 19 patients and decreased for 2 others. Of the remaining 5, 3 died before the results were known and the other 2 were still under observation.

The author emphasizes the importance of securing a new line of weight bearing to relieve and correct deformity. The osteotomy must be slightly oblique in the frontal plane beginning on the lateral surface of the femur 1 fingerbreadth below the trochanteric tubercle and pass upward and inward parallel to the under surface of the neck of the femur. The bone is usually divided above the lesser trochanter.

Postoperative fixation is secured by traction, the lower fragment being constantly abducted. No plaster is used throughout the after-care; thus a painful swollen thigh and a stiff knee are avoided. The distal fragment seldom slips outward, and if it does, it may be replaced with the patient under anesthesia. King (T.) deplors the fact that such a useful procedure requires so long a period of immobilization (from twelve to sixteen weeks) to secure union. He does not advocate this operation for patients past 60 years of age. [ED. NOTE: There is need for intensive study of large series of cases of osteoarthritis of the hip joint. Some attempt should be made to classify them on a more satisfactory basis in terms of the criteria and indications necessary to establish a definite method of therapy. It seems that the indication for certain procedures is at the moment haphazardly and arbitrarily drawn and that little has been done in the way of studying each patient in the light of the precise symptom complex and pathologic picture.]

XV. CONDITIONS INVOLVING THE KNEE JOINT

Torn Semilunar Cartilage.—Ferguson and Thompson⁴⁴⁷ review 100 cases of internal derangement of the knee and find that in 65 the derangement was due to a tear of the semilunar cartilages. There was a ratio of 31 injuries of the internal cartilage to 1 injury of the external cartilage, and the bucket handle type of tear occurred in almost half the cases.

447. Ferguson, L. K., and Thompson, W. D.: Internal Derangements of the Knee Joint: Analysis of One Hundred Cases with Follow-up Study, *Ann. Surg.* 112:454-470 (Sept.) 1940.

There were 31 bucket handle tears, 18 anterior tears, 10 midportion tears and 6 posterior tears. In an additional 13 cases a loose internal semilunar cartilage frequently was associated with a hypertrophied infrapatellar fat pad; in cases of this condition the authors conclude that it is best to remove both the fat pad and the cartilage but that the symptoms are probably more often due to the fat pad than to the loose cartilage.

Vinke ⁴⁴⁸ agrees with Ferguson and Thompson that the bucket handle tear is the most common type and that the internal cartilage is injured more frequently than the lateral cartilage. In his series there was a ratio of 15 injuries of the internal cartilage to 1 injury of the external cartilage.

No new light that would permit a more accurate preoperative diagnosis has been shed on the subject of symptoms produced by tears of cartilage. The history of pain, effusion and locking of the knee after an injury in which the leg is abducted and externally rotated is presumptive evidence of torn cartilage. The type of tear cannot be differentiated, and in many cases only the diagnosis of internal derangement can be made. Vinke, as well as Ferguson and Thompson, points out that the symptom of locking of the knee is absent in about 30 per cent of the cases of torn semilunar cartilage.

Various roentgen studies of the knee joint were made during 1940 in an attempt to gain accuracy in the diagnosis of injuries of the meniscus. Evans ⁴⁴⁹ and Krogdahl ⁴⁵⁰ report their observations with the use of Nordheim's technic. To use this method of examination a padded cone is placed against the side of the knee opposite the meniscus that is to be demonstrated in the roentgenogram. The other end of the cone is placed against the examiner's chest, and the leg is forcibly abducted (or adducted, as the case may be). The basis of this method is that the joint space, which is only a potential space, is opened and a temporary vacuum formed in the joint on the side opposite the cone. This vacuum appears in the roentgenogram as a clear area, and within it can be observed the triangular outline of the meniscus. The roentgen exposure should be made after about five seconds of application of the abducting (or the adducting) force. If a longer time is consumed before exposure, the vacuum will have filled with fluid and the meniscus will not be demonstrated.

Krogdahl found Nordheim's method helpful in making the diagnosis in 4 cases of luxation of the medial meniscus. In 3 of the cases the

448. Vinke, T. H.: Ligamentous and Cartilaginous Injuries of the Knee, *J. Med.* **21**:23-26 (March) 1940.

449. Evans, W. A., Jr.: Roentgenological Demonstration of True Articular Space, with Particular Reference to the Knee Joint and Internal Semilunar Cartilage, *Am. J. Roentgenol.* **43**:860-864 (June) 1940.

450. Krogdahl, T.: Roentgenologic Diagnosis of Luxation of the Semilunar Cartilages Without the Use of a Contrast Substance, *Acta radiol.* **21**:335-342, 1940.

findings were verified at the time of operation. He concludes that if the joint space is at all visible with the use of this method effusion is not present even in the smallest degree.

Evans found that the internal semilunar cartilage could be demonstrated in only 70 per cent of normal knees by the use of Nordheim's method. In the remaining 30 per cent, the true joint space was not revealed. He believes that this method will not always, or even usually, yield conclusive results. Only gross lesions will show up as irregularities in the semilunar cartilage; and since the method cannot be used in the presence of effusion, it is of value only in cases in which the joint is normal or in cases in which there is chronic damage of the semilunar cartilage. The technic may be of value in determining whether ligaments are relaxed, but only after comparison with the ligaments of the opposite knee.

Lindblom ⁴⁵¹ briefly reviews roentgen studies of the knee joint and tabulates the various contrast mediums which have been used in the past for such studies. He expresses the opinion that the use of iodized oil and of colloidal thorium dioxide should be condemned because of their irritating qualities. If iodized water-soluble salts in nonirritating form are used as contrast mediums, they are as good for the purpose as air or oxygen. He believes that two mediums should not be used together, since this only adds to the difficulty of diagnosis. The roentgen evidences of a lesion in the meniscus are: (1) contrast filling of a fissure, (2) partial defect of the meniscus, a reduction of its prominence or a blunting of its edge and (3) interposition of meniscal substance.

In 75 roentgen studies of the knee joint, using 9 cc. of a 35 per cent solution of diodrast as the contrast medium, Evans was able to diagnose lesions of the meniscus in 43 cases. Surgical intervention was performed in 27 of the 43 cases, and in 25 the diagnosis was confirmed at operation. By examination of ordinary roentgenograms of the 27 joints with known damage to the semilunar cartilages, Evans discovered the presence of an osteophyte on the margin of the tibia and a narrowed joint space in 24. In all but 1 case the arthrosis (arthronos; arthritis deformans) was on the side affected by the injury of the meniscus. He concludes that such osteophytes appear several months or years after the initial injury and that the tendency toward their development increases with age. He believes that the arthrosis is secondary to the injury of the meniscus and that by comparison of the affected knee with the normal knee the condition may be demonstrated at an early stage. [ED. NOTE: No new information has been added recently to the knowledge of the management

451. Lindblom, K.: Roentgenographic Symptoms of Meniscal Lesion: Question of Connection Between Meniscal Lesion and Arthrosis, *Acta radiol.* **21**:274-285, 1940.

of injuries of the semilunar cartilages. All authors agree that early treatment should be conservative, with reduction by manipulation or traction followed by immobilization for six to eight weeks. Surgical intervention is commonly reserved for those cases in which repeated episodes of disability occur or for those in which the initial locking cannot be reduced.]

Ferguson and Thompson observe little difference in end results in their group of cases when they compare the group in which only the torn tags were removed with the group in which the entire cartilages were excised.

Bohlman⁴⁵² describes an elaborate program of preparation of the patient for removal of semilunar cartilages. This program includes eradication of foci of infection, a test for wound healing, a test with Burky's toxin and perhaps a preoperative course of treatment with Burky's toxin to raise the immunity to staphylococcic infection, a blood platelet count and a twenty-four hour preparation of the skin. He suggests that local anesthesia should be employed at operation and that high frequency electrocautery but not a tourniquet should be used. He washes out the joints with a solution of procaine hydrochloride or physiologic solution of sodium chloride and finally injects air into the joints to cause compression and hemostasis. [ED. NOTE: This technic seems unnecessarily complicated, although the end results in the 50 cases reported by Bohlman were good.]

Bonadeo Ayrolo⁴⁵³ describes a clamp which he purchased in Vienna, a small guillotine, a meniscus hook and a separator, which he states are of value in operating on the knee joint.

After surgical procedures for torn semilunar cartilages there is frequently a period of disability that lasts for six months to one year. This is noted by Ferguson and Thompson, but they note also that the disability gradually disappears and that the patient's age and the duration of symptoms have no effect on the operative result. They point out that surgical intervention itself does not produce arthritis but that a persistent disability may be a factor in the production of the disease.

In writing about injuries of the semilunar cartilage, Smith and King⁴⁵⁴ describe what they believe to be a hitherto undescribed lesion of the knee joint. The symptoms of this lesion have their onset with an injury and are similar to those produced by a torn meniscus, except that

452. Bohlman, H. R.: Improved Technic for Removal of Semilunar Cartilage and Postoperative Treatment, *J. A. M. A.* **115**:2243-2246 (Dec. 28) 1940.

453. Bonadeo Ayrolo, A.: Personal Statistics on the Surgical Treatment of Meniscus Lesions of the Knee from 1933 to the Present: Special Technique and Instruments, *Día méd.* **12**:866-868 (Sept. 23) 1940.

454. Smith, A. DeF., and King, B. B.: Injury to the Femoral Articular Cartilage by the Medial Meniscus, *Surg., Gynec. & Obst.* **71**:679-683 (Nov.) 1940.

locking is seldom observed. At the time of operation there is found in the medial condyle of the femur a depressed region which corresponds in position and outline to the anterior end of the medial meniscus. Converging on this region is a pannus of vascular tissue growing in from the margin of the medial condyle. Although Henderson and others have drawn attention to erosion of the condyles that may occur from pressure exerted by a torn semilunar tag, Smith and King believe that theirs is the first description of such a depression without gross evidence of damage to the semilunar cartilage and that the depression is due to a sudden injury to the extended knee by which the meniscus is suddenly pressed against the femoral articular cartilage. Of 10 cases that they have observed, they report 9; in each case the patient was relieved of symptoms by excision of the medial semilunar cartilage.

Tears of the Cruciate Ligaments.—Injuries to the cruciate ligaments are comparatively rare; but when they occur, the anterior ligament is torn more frequently than the posterior. In only 4 of the 100 cases of internal derangement of the knee in the series of Ferguson and Thompson was there an injury of the cruciate ligament, and in 3 of these cases the injury was associated with other pathologic changes in the knee joint. Interestingly enough only 1 of the patients underwent repair of the cruciate ligament, and yet all the patients regained good use of their knees and returned to active sports. This outcome is in line with Vinke's statement that the lateral ligaments are important from the standpoint of stability but that a knee can function well without a cruciate ligament. He advises immobilization for three months followed by the use of a brace for six months as treatment for acute injuries of a cruciate ligament. Surgical intervention is reserved as a last resort, for reconstruction is rarely necessary if the other ligaments and the muscles around the knee are functioning well. [ED. NOTE: By inference it may be said that Ferguson and Thompson would concur in this opinion.]

An interesting method of substituting for a torn anterior cruciate ligament is described by Tees.⁴⁵⁵ Through an incision on the antero-lateral aspect of the thigh a strip of fascia lata 10 inches (25 cm.) long is turned down and left attached to the tibial tuberosity in front of the head of the fibula. A hole is then drilled through the lateral tuberosity of the tibia, starting at the point of attachment of this fascial strip and emerging in the joint at the tibial spine. A second hole is then drilled through the lateral condyle of the femur and the fascial strip is threaded through the channel in the tuberosity of the tibia and out of the joint through the channel in the lateral condyle of the femur. The free

455. Tees, F. J.: New Method of Repairing the Anterior Crucial Ligament of the Knee, *Canad. M. A. J.* 42:214-216 (March) 1940.

end of fascia is then passed through the hole drilled in the head of the fibula and sutured taut. Tees believes this method of repair a valuable one, for it eliminates opening of the knee joint. Passing the fascial strip through the drill channels is difficult but is accomplished by first inserting a strand of wire through the lower channel and grasping it with a laryngologist's alligator forceps that has been passed into the upper drill channel. After the wire is drawn through, the fascial strips can be attached and pulled through. Tees reports 1 case in which the result from this procedure was good.

Osteochondritis Dissecans.—Berkheiser⁴⁵⁶ draws attention to multiple lesions, like those of osteochondritis dissecans, that are found in the patella and the condyles of the femur in aged persons with osteoarthritis. These are yellowish gray oval areas of chondromalacia that are well demarcated and may be covered with exfoliating cartilage. Loose bodies may form and result in a cavity with a fibrous tissue base overlying eburnated bone. Microscopically, the loose bodies are similar to those of osteochondritis dissecans as seen in younger persons. The author recommends surgical intervention for those patients whose advanced age is not a contraindication. For those patients for whom operation is not advisable, a period of immobilization is recommended in the hope that the loose bodies will attach to the synovia and the episodes of locking will thereby be reduced in frequency.

Interesting observations on the fate of foreign bodies within a joint are presented by Hultén and Gellerstedt.⁴⁵⁷ Minute pieces of cartilage were kept in physiologic solution of sodium chloride at body temperature for several months with only occasional evidence of liquefaction. From this phenomenon they conclude that autolysis plays little or no part in removing blood clots and small cartilaginous pieces from joint cavities. They then injected sterile suspensions of cartilaginous scrapings into knee joints of animals and observed that the foreign particles first migrated to the suprapatellar pouch or to the posterior compartment; they disappeared quickly from the former location and slowly from the latter. The small particles were phagocytosed, and the larger ones were enveloped by synovial cells growing around them. If large pieces were enveloped, the resulting lump in the synovial membrane could not be leveled but could be torn loose as a foreign body. The synovial membrane reacted to the foreign bodies by hyperemia and increase in histiocytes. This reaction was followed by a decrease in histiocytes but an increase in synovial connective tissue. Eventually fibroplastic synovitis

456. Berkheiser, E. J.: Osteochondritis of the Knee in Aged Patients, *S. Clin. North America* 20:97-102 (Feb.) 1940.

457. Hultén, O., and Gellerstedt, N.: Loose Bodies in the Knee and Resorption of Worn-Off Cartilaginous Fragments Simulating Dendritic Synovitis, *Acta chir. Scandinav.* 84:1-29, 1940.

resulted, which the authors term "synovitis chondrodetrítica." This type of synovitis occurs regularly in chondromalacia patellae, osteochondritis dissecans, arthritis deformans and intra-articular fractures. It results in pain, but rest gives relief by reducing the formation of new particles and after even a few days' rest the acute stage of cartilage digestion is over. The authors state that when surgical intervention for these conditions affords relief it does so by eradication of the source of cartilaginous detritus.

Osteomatosis.—Borsotti⁴⁵⁸ records the histologic observations in a case of osteomatosis in which total synovectomy and arthrodesis were performed because of extreme pain in the knee. The synovial membrane was the seat of marked hyperplastic reaction with an increase in blood vessels. There was no evidence of inflammatory reaction, either acute or chronic. Loose bodies were palpated that arose from metaplastic ossification of the abundant young connective tissue that was found in the synovial villi. [ED. NOTE: These microscopic observations appear similar to those in the synovitis chondrodetrítica of Hultén and Gellerstedt.]

The author believes that from the histologic point of view chondromatosis, osteochondromatosis and osteomatosis are three separate diseases. [ED. NOTE: They are probably all related and differ only in the degree of metaplasia.]

Recurrent Dislocation of the Patella.—Marottoli⁴⁵⁹ divides recurrent dislocations of the patella into three types, traumatic, congenital and habitual, according to the definiteness of the traumatic factor and the degree of morphologic change. Bony changes are present in dislocations of the congenital type but are rare in those of the habitual type. Changes in the soft tissue are most common in dislocations of the habitual type; the most frequent change is elongation and relaxation of the patellar tendon with upward displacement of the patella. The author states that reconstruction of the soft tissue and operation on the bone will not cure the condition. In the 5 reported cases he resorted to extirpation of the patella and obtained good results.

Urrutia Urrutia⁴⁶⁰ reviews 30 cases of recurrent dislocation of the patella in which the patients were treated by Putti. All the methods of treatment described in the literature were used in treating these patients, who were divided into groups according to treatment; good results were

458. Borsotti, P. C.: Osteomatosis of the Knee: Case, Chir. d. org. di movimento 25:427-435 (April) 1940.

459. Marottoli, O. R.: Patellectomy in Therapy of Recidivating Dislocation, Bol. y trab. Acad. argent. de cir. 24:286-313 (June 5) 1940.

460. Urrutia Urrutia, C.: Surgical Therapy of Congenital Luxation of the Patella, Rev. ortop y traumatol. 9:203-246 (Jan.) 1940.

obtained in each group. The author finds that the best results were obtained in the group in which mixed types of procedures were used according to the pathologic changes observed at the time of operation. He concludes that the incision for repair should be large enough to permit a general view of the field, so that the plan of operative procedure can be changed if the condition observed makes it necessary.

Roberts ⁴⁶¹ expresses the opinion that excision of the patella is not of benefit in the treatment of recurrent dislocations, because the remaining tendon of the quadriceps muscle will often become dislocated.

Hereditary Arthrodysplasia.—Hereditary arthrodysplasia is represented clinically by hereditary changes in the knee together with the presence of rudimentary nails. The patella is dislocated outward, and the knee is broad, with an easily palpable intercondylar notch. The quadriceps muscle and tendon are narrow and weak, and although the motions of the knee are normal, active extension is weak.

Venable ⁴⁶² dissected a knee joint in which the pathologic change had previously been diagnosed as hereditary arthrodysplasia. The most significant finding was congenital absence of the anterior cruciate ligament; all other changes seemed secondary to this. The author believes that the absence of the one cruciate ligament allowed the tibia to rotate externally. This action led to splaying of the quadriceps tendon, lateral dislocation of the patella and resultant hypertrophic change. Bennett and Bauer ⁴⁶³ produced similar changes in rabbits by dislocating the patella outward and suturing it in its new location. No explanation is offered for the dystrophy of the nails which is associated with congenital absence of the anterior cruciate ligament.

Excision of the Patella.—Roberts briefly reviews the history of excision of the patella for fracture and points out that the first of such operations was performed in 1890 by Althmann. Subsequent to that operation there were sporadic reports of similar treatments, and finally a general interest arose in the procedure. The operation, according to the author, now is accepted in England as the most satisfactory method of treatment. It eliminates the irregularities of the articular surface that follow the treatment of fracture of the patella by any other method, and thus it does not predispose to osteoarthritis. Furthermore, recovery is seldom slow and incomplete after excision of the patella.

The secret of success in extirpating a fractured patella lies in the fact that the primary necessity is suturing of the expansions of the tendon

461. Roberts, N.: Excision of the Patella, *M. Press* 204:389-391 (Nov. 13) 1940.

462. Venable, J. H.: Structure of the Knee Joint in Hereditary Arthrodysplasia, *South. Surgeon* 9:345-350 (May) 1940.

463. Cited by Venable.⁴⁶²

of the quadriceps muscle which were torn at the time of injury. The fracture of the patella is only a part of the injury, and provided the expansions are firmly sutured without lengthening the tendon, normal extension power is restored even if the patella is removed.

Roberts points out some of the disadvantages of excision of the patella. The operation removes the protection that the patella offers to the articular surfaces of the knee joint and to the tendon of the quadriceps muscle. However, the advantages of the operation offset the disadvantages, and he recommends its use. Total excision of the patella is recommended for comminuted fracture, but for young men patients suture of the fragments when they are of equal size is the procedure of choice. The removal of one fragment when it is smaller than the other likewise gives good results and has all the advantages of total excision without its disadvantages. Each case should be judged separately.

Roberts believes that good results can be expected from excision of the patella in osteoarthritis when the process involves mainly the patello-femoral articulation. He doubts its advisability for chronic rheumatoid arthritis. Tuberculosis, chronic osteomyelitis, Paget's disease, osteomalacia and traumatic osteochondritis are other indications for the operation.

Rupture of the Tendon of the Quadriceps Muscle.—Rupture of the tendon of the quadriceps muscle occurs by direct or indirect violence, and according to McMaster⁴⁶⁴ the rupture occurs at the insertion of the tendon, at the musculotendinous junction, through the belly of the muscle or at the origin of the muscle. In diseased tendons spontaneous rupture may occur.

Conway⁴⁶⁵ points out that the pathognomonic sign of a suprapatellar rupture is absence of fulness of the quadriceps pouch. If the rupture is below the patella, there is an upward shift of the patella, and in either case extension of the knee is weak or absent. Good results follow operative repair.

Xanthoma.—Willenegger⁴⁶⁶ collected 35 cases of xanthoma of the joints from the literature. In 31 cases the xanthoma was in the knee joint, and in 4 it was in the ankle. In 23 of the cases the xanthoma was a solitary tumor; in 7 cases the growth was diffuse; in 2 there were multiple tumors, and in 3 the solitary and the diffuse type were combined.

464. McMaster, P. E.: Tendon and Muscle Ruptures: Clinical and Experimental Studies on Causes and Location of Subcutaneous Ruptures, *J. Bone & Joint Surg.* **15**:705-722 (July) 1933.

465. Conway, F. M.: Rupture of the Quadriceps Tendon with Report of Three Cases, *Am. J. Surg.* **50**:3-16 (Oct.) 1940.

466. Willenegger, H.: Intra-Articular Xanthomas with Special Reference to Knee Joints, *Deutsche Ztschr. f. Chir.* **253**:97-124, 1940.

To these cases from the literature the author adds 3 cases of solitary xanthoma of the knee joint. He describes the microscopic structure of the tumors and calls one of them a "xanthoma variant" because of the presence of giant cells. [ED. NOTE: Giant cells are a part of the picture of xanthoma but are not always present. The fact that they are present should not change the diagnosis of xanthoma.]

Cederlund ⁴⁶⁷ reports 2 cases of xanthoma of the knee. The symptoms and findings of this type of growth are summed up as (1) palpable or visible tumor medial to the apex of the patella, (2) pain, (3) hydrops [ED. NOTE: Yellowish brown or chocolate-colored fluid may be found by aspiration.] and (4) functional disturbances such as locking or impaired motion. The author states that increased blood cholesterol has been reported as present in only half of the cases. [ED. NOTE: Galloway, Broders and one of us (R. K. G.⁴⁶⁸) point out that there is usually a disturbance in the ratio of cholesterol to cholesterol esters in patients with xanthoma.]

Cederlund states that in only 1 of 40 cases was diagnosis of xanthoma made preoperatively and that the growth in this 1 case was a recurrent tumor. Xanthoma usually is diagnosed as loose body, torn cartilage, lipoma or osteochondroma. All authors agree that it is benign, even though Willenegger describes 1 case in which the tumor tissue infiltrated between the cartilage and the bone of the femur. Metastasis from xanthoma has not been recorded.

Cysts of Semilunar Cartilages.—Kulowski ⁴⁶⁹ reports 19 cases of cyst in the meniscuses of the knee and reviews the theories of causation. He states that the cardinal point in diagnosis is the movement of the mass with the tibia in flexion and in extension. The mass moves on a level with the line of the joint, and the cyst is most prominent on complete extension. The author reports 3 cases of malformed meniscus associated with cyst and states that the number of cases of cyst of the semilunar cartilage reported previous to 1940 is 276.

King ⁴⁷⁰ reports that in his previous papers he concluded that the process of formation of a cyst in the meniscuses was not degenerative because the cells were well developed in the mucoid area, the nuclei did

467. Cederlund, H.: Two Cases of Intra-Articular Xanthoma in the Knee, *Acta chir. Scandinav.* **84**:143-154, 1940.

468. Galloway, J. D. B.; Broders, A. C., and Ghormley, R. K.: Xanthoma of Tendon Sheaths and Synovial Membranes: Clinical and Pathologic Study, *Arch. Surg.* **40**:485-538 (March) 1940.

469. Kulowski, J.: Meniscus Cyst of the Knee Joint, *J. Missouri M. A.* **37**: 503-508 (Dec.) 1940.

470. King, E. S. J.: Formation of Ganglia and Cysts of Menisci of Knee: Observations on Golgi Apparatus, *Surg., Gynec. & Obst.* **70**:150-156 (Feb.) 1940.

not indicate a degenerative process and there were droplets of secretion in the cytoplasm of the cells. By special staining of the Golgi apparatus in freshly collected operative specimens, the author found that there was hypertrophy of the cellular structure. He concludes that a cyst of this type is formed by excess secretion and is therefore the result of over-activity and not the result of a degenerative process.

Synovectomy.—Carruthers⁴⁷¹ reviews the history of synovectomy and reports 34 such operations performed on 28 patients. Two of the bilateral operations were performed for chronic hypertrophic villous arthritis, and 4 were done for chronic arthritis. Eight of the unilateral operations were done for chronic synovitis, and the remaining 14 were performed for chronic infectious arthritis. The ages of the patients varied from 18 to 69 years, with the greatest number in the age group of 30 to 40 years. The operation consisted of removal of all the diseased layers of the synovial membrane together with removal of the infrapatellar fat pad and of the menisci when they were involved. Traction was applied for ten days, but motion to the point of pain was started forty-eight hours after operation. The author states that synovectomy is a useful operation, and in his group of cases 75 per cent of the patients experienced marked relief from symptoms. Pain and discomfort always were relieved; the average gain in motion was at least equal to what it was before surgical intervention, and in 50 per cent of the cases it was greater. More than 75 per cent of the patients showed general improvement in the arthritis, but whether this relief was due to removal of a focus of infection could not be determined. In 4 of the author's cases ankylosis resulted.

Ankylosis.—Elkins⁴⁷² describes an apparatus for forcibly flexing the knees of patients who have fibrous ankylosis in extension. The toes are held to the floor by straps, and a bar fits across the popliteal spaces. The knees are gradually flexed by lowering the body weight. The apparatus is easily constructed and can be built across a door frame.

The late Willis Campbell⁴⁷³ reported 2 cases in which arthroplasty of the knee was performed with vitallium plates fitted over the lower end of the femur. The results were considered disappointing, possibly owing to the creation of too narrow a joint space, which the author felt should have been $\frac{3}{4}$ inch (2 cm.). He reported that he was devising a

471. Carruthers, F. W.: Synovectomy of the Knee Joint, *South. M. J.* **33**:550-552 (May) 1940.

472. Elkins, E. C.: Simple Device for Forced Flexion of the Knee, *Arch. Phys. Therapy* **21**:468-469 (Aug.) 1940.

473. Campbell, W. C.: Interposition of Vitallium Plates in Arthroplasties of the Knee: Preliminary Report, *Am. J. Surg.* **47**:639-641 (March) 1940.

plate to cover the upper end of the tibia rather than the lower end of the femur, but at the time of his report he had not used the plate in any case.

Flexion Deformities.—Preston ⁴⁷⁴ describes a technic for transplantation of the attachment of the patellar tendon in cases of flexion deformity of the knee. The flexion deformity must be corrected first, after which the attachment of the tendon is transplanted distally $\frac{1}{8}$ inch (0.32 cm.) for each degree of fixed flexion deformity. The author claimed that by means of a double dovetail at the point of transplantation, active motion could be started immediately after operation.

Chandler ⁴⁷⁵ reports that because he had difficulty in maintaining the position of the transplanted block of bone he devised a new operative procedure. The patella is transfixed by wire on heavy braided silk and is wired into a normal position with the joint by passing the other end of the wire through a hole drilled beneath the tubercle of the tibia. Narrow strips of the anterior portion of the patellar tendon then are elevated and used to lace through the redundant margins of the tendon. The author believes that this operation reestablishes the normal leverage of the patella by a procedure less extensive and shorter than other methods. It eliminates the possibility of arrest of growth in the epiphysis of the tibia, and the patellar tendon is increased in size and strength by the plication.

New Operations and Technics.—Resection of the Knee Joint: Heyn ⁴⁷⁶ describes a new technic for resection of the knee. The surfaces of the femur and the tibia are fitted together by a curved osteotomy, and the patella is then countersunk as a graft across the joint. The patella is shaped more or less like a keystone wedge.

Dogliotti ⁴⁷⁷ describes the use of a portion of the upper end of the tibia as a graft across the resected knee joint. The articular surfaces of the femoral condyles are removed, and the lateral portions of the articulating surfaces are resected. The central portion of the tibial surface is freed but left attached by the cruciate ligaments. This piece of bone then is swung around and inserted into a groove anteriorly across the joint line. The author believes that a graft of this type will prove more efficient as a result of unimpaired circulation through the vessels in the cruciate ligaments than grafts of other types. He advises

474. Preston, R. L.: Immediate Restoration of Active Extension of Knee Following Flexion Deformities, *Am. J. Surg.* **50**:303-305 (Nov.) 1940.

475. Chandler, F. A.: Patellar Advancement Operation: Revised Technique, *J. Internat. Coll. Surgeons* **3**:433-435 (Oct.) 1940.

476. Heyn, W.: Technique of Resection of the Knee, *Zentralbl. f. Chir.* **67**: 110-113 (Jan. 20) 1940.

477. Dogliotti, A. M.: New Method for Intra-Articular Arthrodesis of the Knee, *J. Internat. Coll. Surgeons* **3**:103-106 (April) 1940.

its use for treatment of paralytic dangling knee, spastic knee and early tuberculosis with the central area of the knee joint unaffected.

Exposure of the Knee Joint: Mader⁴⁷⁸ describes a technic of exposure of the knee joint in which the patella is resected. Studies on 20 cadavers failed to show any effect on extension of the knee when the patella was removed. [ED. NOTE: This seems a rather drastic procedure to advise in most cases of arthrotomy of the knee. The increase in the number of authors recommending removal of the patella for various reasons would seem to indicate, however, that the patella is not vital to function of the knee joint.]

XVI. CONDITIONS INVOLVING THE FOOT AND ANKLE

Foot Imbalance in Children.—Observation of a large number of cases leads Bloxsom⁴⁷⁹ to conclude that the child's foot develops most rapidly between the ages of 1 and 4 years. Some children continue in the non-developmental stage, and their feet do not respond to corrective measures. [ED. NOTE: This seems a broad statement, since it is well known that the rate of development is not the same in all persons. Only observation over a number of years will demonstrate the accuracy or error of this statement.] The importance of overweight as the cause of distortion of the ankle and the foot in young children is emphasized by Caldwell.⁴⁸⁰ He urges dietary measures and the use of corrective shoes in cases in which overweight is a factor.

Foot Strain and Painful Feet.—Steindler⁴⁸¹ discusses the causation of flatfoot and stresses that the muscles are first relaxed before there can be relaxation of the ligaments and depression of the arch. [ED. NOTE: The question of whether faulty architecture precedes the relaxation and the giving way of the supporting muscles due to overwork or whether the faulty architecture follows the giving way of the muscles is still debatable. The preponderance of evidence seems to indicate that faulty architecture is the primary cause and muscle relaxation secondary.] Cozen⁴⁸² stresses the importance of manipulation in the treatment of painful conditions of the feet. The manipulations recommended are in the direction of supination, pronation, dorsiflexion,

478. Mader, V. O.: New Approach to the Knee Joint, *Canad. M. A. J.* 42: 17-18 (Jan.) 1940.

479. Bloxsom, A.: Study of Feet of Infants and Children, *Am. J. Dis. Child.* 59:45-47 (Jan.) 1940.

480. Caldwell, G. A.: Overweight as Cause of Knee and Ankle Deformities in Babies, *Tri-State M. J.* 12:2426 (Feb.) 1940.

481. Steindler, A.: Anatomical and Physiological Conditions of Feet, *Mil. Surgeon* 86:379-383 (April) 1940.

482. Cozen, L.: Foot Strain: Simple Method of Treatment, *Mil. Surgeon* 86:290-292 (March) 1940.

plantar flexion and rotation. These manipulations are followed by simple balancing of the sole of the shoes in various ways. [ED. NOTE: While unquestionably beneficial in cases in which the condition is mild, it seems doubtful whether manipulation can be expected to accomplish much in symptom-producing conditions of the feet with faulty architecture.] Arkin⁴⁸³ reports excellent results obtained by the use of Whitman foot plates. [ED. NOTE: Although excellent results are being obtained by the use of rigid plates, supports made of more resilient material, such as sponge rubber, leather or celluloid, are today largely replacing metal supports. They are less difficult to adjust and on the whole more comfortable while just as efficient.]

Operative Correction of Flatfoot.—There seems to be a definite trend toward surgical intervention in the correction of flatfoot, if the condition fails to respond to well directed conservative treatment. White⁴⁸⁴ advocates the correction of flatfoot by two osteotomies. One of these is performed on the medial border of the foot for the purpose of shortening this border; the other is performed on the lateral border of the foot for the purpose of lengthening that border. White reports excellent results. [ED. NOTE: While residual anomalies of the feet which fail to respond to treatment frequently require arthrodesing types of operations, it is well to avoid these if possible. The method of White, which does not enter any joint, seems to be a step away from such arthrodesing operations. It is well to bear in mind that many unbalanced feet can be corrected without operation on any bone by means of the methods of Lowman⁴⁸⁵ and Young,⁴⁸⁶ which are based on bringing about an alteration in the action of the tendon of the tibialis anterior muscle.] These operations are discussed by Burke⁴⁸⁷ in a thorough way.

Morton's Toe.—The formation of a neuroma on the fourth plantar digital nerve is suggested by Betts⁴⁸⁸ as the cause of Morton's toe on the basis of 1 case observed. [ED. NOTE: Dudley Morton has suggested that the irritation of this nerve might well be the cause of metatarsalgia. Since metatarsalgia does not always affect the same toe, it still seems

483. Arkin, A. M.: Results of Treatment of Weak Foot by Whitman Plates, *M. Rec.* **152**:392-393 (Dec. 4) 1940.

484. White, J. W.: Congenital Flat Foot: New Surgical Approach, *J. Bone & Joint Surg.* **22**:547-554 (July) 1940.

485. Lowman, C. L.: An Operative Method for Correction of Certain Forms of Flatfoot, *J. A. M. A.* **81**:1500-1502 (Nov. 3) 1923.

486. Young, C. S.: Operative Treatment of Pes Planus, *Surg., Gynec. & Obst.* **68**:1099-1101 (June) 1939.

487. Burke, G. L.: Surgical Treatment of Flat Feet, *Canad. M. A. J.* **43**:327-331 (Oct.) 1940.

488. Betts, L. O.: Morton's Metatarsalgia Neuritis of Fourth Digital Nerve. *M. J. Australia* **1**:514-515 (April 13) 1940.

reasonable to explain this syndrome by pressure on the digital nerves between the heads of the metatarsal bones when the transverse arch is depressed or reversed.]

Hallux Valgus.—Hallux valgus is a comparatively common and frequently incapacitating and painful condition. McElvenny and Thompson⁴⁸⁹ report 100 cases of simple exostosectomy for the relief of this condition. A bunion can occur without hallux valgus. When this situation exists, simple excision of the exostosis is all that is necessary. When hallux valgus is associated with enlargement of the joint of the great toe, correction of the lateral deviation of the great toe is necessary for a successful result. Several types of suggested operations are available for the correction of hallux valgus, of which the Keller or Schanz operation is probably the best.⁴⁹⁰ [ED. NOTE: It should be borne in mind that when pes varus of the first metatarsal bone is present, this condition must be corrected as well as the valgus position of the great toe, and for this type of case the operation of Lapidus⁴⁹¹ seems the procedure of choice.]

Hallux Rigidus.—Hallux rigidus or dorsal bunion is a condition which causes considerable discomfort in walking and at times is definitely incapacitating. The causation of this condition is obscure, but fundamentally it is due to faulty weight bearing from various causes.⁴⁹² A variety of procedures is suggested for the relief of hallux rigidus. Several conservative procedures are outlined for the relief of the condition, including the wearing of a heavy-soled shoe and a metatarsal bar.⁴⁹³ Several surgical procedures are offered, one of which includes reshaping of the metatarsal heads and resection of the proximal end of the first phalanx of the great toe, that is, the Keller operation. Ankylosing the joint of the great toe in 15 degrees of dorsiflexion is suggested by Thompson and McElvenny.⁴⁹⁴ [ED. NOTE: The latter suggestion does not recommend itself greatly because the cockup position of the toe would be likely to cause the tip of the shoe to press against the nail,

489. McElvenny, R. T., and Thompson, F. R.: Clinical Study of One Hundred Patients Subjected to Simple Exostosectomy for Relief of Bunion Pain. *J. Bone & Joint Surg.* **22**:942-952 (Oct.) 1940.

490. Schein, A. J.: Keller Operation: Partial Phalangectomy in Hallux Valgus and Hallux Rigidus: Report of Fifty-Five Operations in Thirty-Two Cases. *Surgery* **7**:342-355 (March) 1940.

491. Lapidus, P. W.: Operative Correction of Metatarsus Varus Primus in Hallux Valgus, *Surg., Gynec. & Obst.* **58**:183-191 (Feb.) 1934.

492. Jack, E. A.: Etiology of Hallux Rigidus, *Brit. J. Surg.* **27**:492-497 (Jan.) 1940.

493. Allan, F. G.: Hallux Valgus and Rigidus, *Brit. M. J.* **1**:579-581 (April 6) 1940.

494. Thompson, F. R., and McElvenny, R. T.: Arthrodesis of First Metatarsophalangeal Joint, *J. Bone & Joint Surg.* **22**:555-558 (July) 1940.

and, furthermore, it seems likely that the angle of dorsiflexion would tend to increase as time goes on, resulting in increased pressure on the tip of the toe.] Lapidus⁴⁹⁵ describes an extensive operation which is necessarily complex to meet comparatively simple conditions. Remodeling of the tarsal heads and resection of a segment from the base of the first phalanx usually give satisfactory results and seem to comprise the operation of choice.

Hammer Toe.—Congenital hammer toe usually involves the fifth toe. The condition can be very troublesome. It is recommended that its correction be brought about by capsuloplasty and transplantation of the tendon of the extensor muscle of the fifth toe into the metatarsal head.⁴⁹⁶ [Ed. NOTE: The fifth toe can be amputated without disturbing the architecture of the foot, and since this procedure is simple and effective, it seems more logical to carry out simple amputation than to do such a complicated operation as recommended.] Taylor⁴⁹⁷ recommends the passing of a Kirschner wire down through the proximal and midphalanges to maintain the position of the bones after arthrodesis of the first interphalangeal joint in the correction of hammer toe. [Ed. NOTE: This method of fixation recommends itself by its simplicity, but it is perhaps not as simple as it seems. Adequate fixation can be secured by a small molded metal splint to permit early use of the feet after operation for the correction of hammer toe, and the advisability of the additional procedure of introducing a wire for fixation is questionable.]

Talipes Cavus.—The evidence presented by Brewster and Larson⁴⁹⁸ clearly points out that the best results can be expected from treating feet affected by talipes cavus by triple arthrodesis and transplantation of the long tendons of the extensor muscles of the toes to the necks of the metatarsal bones. Cole,⁴⁹⁹ on the other hand, recommends a method of treatment which consists of transplanting the long tendons of the extensor muscles of the toes into the cuneiform bones so that their pull will aid the tibialis anterior muscle in dorsiflexing the ankle. Brewster and Larson state that for the relief of cavus, callus, pain and to a certain extent cockup toes, a triple arthrodesis alone is efficient.

495. Lapidus, P. W.: "Dorsal Bunion:" Its Mechanics and Operative Correction, *J. Bone & Joint Surg.* **22**:627-637 (July) 1940.

496. Lantounis, L. A.: Congenital Subluxation of Fifth Toe and Its Correction by Periosteocapsuloplasty and Tendon Transplantation, *J. Bone & Joint Surg.* **22**:147-150 (Jan.) 1940.

497. Taylor, R. G.: Operative Procedure for Treatment of Hammer-Toe and Claw-Toe, *J. Bone & Joint Surg.* **22**:608-609 (July) 1940.

498. Brewster, A. H., and Larson, C. B.: Cavus Feet, *J. Bone & Joint Surg.* **22**:361-368 (April) 1940.

499. Cole, W. H.: Treatment of Clawfoot, *J. Bone & Joint Surg.* **22**:895-908 (Oct.) 1940.

This operation when done for claw foot must bring about the following results: (1) The astragalus must be reshaped to elevate the forefoot, so as to flatten the arch; (2) the os calcis must be relieved of its calcaneus position and set back to reduce contracture and increase leverage of the tendo achillis, and (3) the foot must be shortened, to relax the tightness of the plantar fascia and also to lessen the cockup position of the toes by relaxing the contracted tendons. These authors describe a modification of the usual triple arthrodesis to accomplish these objectives better. Cole further states that if bone deformity of marked degree exists, the removal of an anterior tarsal wedge of bone is indicated. This is removed anterior to the midtarsal joint through the cuneiforms, scaphoid and cuboid, thereby preserving the lateral motion of the foot and correcting the deformity. [ED. NOTE: These reports of the treatment of patients with talipes cavus are excellent and come from reliable sources. The original articles should be read.]

Sesamoid Bones.—Miller and Arendt⁵⁰⁰ report 3 cases in which there was aseptic necrosis of the head of the first metatarsal bones. They consider that the causative factor was concentration of weight bearing on the head of the metatarsal bones due to backward displacement of the sesamoid bones. The effect of such backward displacement of the sesamoid bones is to deprive the head of the first metatarsal bone of the protection which these bones normally give it and to allow the head of the bones to be subjected to repeated trauma. The conservative treatment suggested is the use of a metatarsal bar and, failing that, removal of part of the proximal phalanx of the great toe (Keller operation). [ED. NOTE: The condition described may be a definite entity, but it strikingly resembles hallux rigidus in appearance and effect.]

March Fractures.—Hansen⁵⁰¹ and Drummond⁵⁰² discuss march fractures. Hansen recommends treatment by a heavy-soled shoe or a plaster cast. [ED. NOTE: There is nothing particularly new in either of these articles.]

Trench Foot and Frost Bite.—Greene⁵⁰³ discusses the causation and the treatment of trench foot. The causative factors, in his opinion, are slowing of the circulation and decrease in the oxygen tension. He suggests the wearing of properly fitting, dry footwear as a prophylactic

500. Miller, L. F., and Arendt, J.: Deformity of First Metatarsal Head Due to Faulty Foot Mechanics, *J. Bone & Joint Surg.* 22:349-353 (April) 1940.

501. Hansen, H.: Hints About Marching Feet, *Mil. Surgeon* 86:592-593 (June) 1940.

502. Drummond, R.: March Fracture: Report on Case Involving Both Feet. *Brit. M. J.* 2:413-414 (Sept. 28) 1940.

503. Greene, R.: Frost-Bite and Trench Foot, *Lancet* 1:393-395 (Feb. 17) 1940.

measure, and he advises against applying heat and rubbing with snow. He suggests protection of the feet and general supportive measures, including rest and warm drinks.

Sprained Ankle.—The treatment of sprained ankle is discussed by several authors. The recommendations vary from simple strapping to extensive use of cold, injections of 2 per cent procaine hydrochloride, use of crutches and massage.⁵⁰⁴ [ED. NOTE: It seems well established that adequate support by proper strapping, use of sinusoidal current and early resumption of function give satisfactory results in the majority of cases.]

Shoes.—Several timely articles are devoted to the qualities necessary to a proper shoe.⁵⁰⁵ [ED NOTE: Unfortunately, there is a definite lack of understanding on the part of physicians of what constitutes a proper shoe and a widespread feeling that the so-called corrective shoe can be recommended on the basis of the claims made by the manufacturer. Improved management of painful conditions in the feet can be anticipated only when physicians familiarize themselves with correct shoeing of the feet and learn that the so-called corrective shoe does not solve the problem of the patient with a symptom-producing foot condition.]

XVII. CONDITIONS INVOLVING THE SHOULDER, NECK AND JAW

Torticollis.—Koster⁵⁰⁶ reports 2 cases of spasmodic torticollis, which is recognized as being stubborn to all forms of treatment. He obtained good results by using large doses of atropine, 3.25 to 8.75 mg. daily. Rugh⁵⁰⁷ believes that spasmodic torticollis is of two main types: one of psychogenic origin and one due to lesions in the brain stem. Over a long period of years he has used plaster fixation of the head followed by support in a brace with satisfactory results. Whiles⁵⁰⁸ stresses that most patients with torticollis are also afflicted with underlying anxiety and social maladjustment. He has had good results with psychotherapy

504. Galland, W. I.: Adhesive Strapping for Sprain of Ankle, *J. Bone & Joint Surg.* **22**:211-215 (Jan.) 1940. Alexander, H. H., Jr.: Treatment of Sprained Ankle, *Am. J. Surg.* **50**:581-584 (Dec.) 1940. Ball, C. R.: Sprained Ankles: Treatment by Novocaine and Adrenalin Injections, *U. S. Nav. M. Bull.* **38**:499-502 (Oct.) 1940.

505. Armstrong, G. W.: Treatment of Painful Feet, *Canad. M. A. J.* **42**:227-231 (March) 1940. Lake, N. C.: The Foot and the Shoe, *M. Press* **203**:220-224 (March 13) 1940. Jones, A. R.: Shoes and Disabilities of Feet, *ibid.* **203**:224-226 (March 13) 1940.

506. Koster, S.: New Guiding Principles for Treatment of Torticollis Spastica (Cerebralis), *Nederl. tijdschr. v. geneesk.* **84**:225-230 (Jan. 20) 1940.

507. Rugh, J. T.: Spasmodic Torticollis: Its Cause and Treatment, *Am. J. Surg.* **49**:490-495 (Sept.) 1940.

508. Whiles, W. H.: Treatment of Spasmodic Torticollis by Psychotherapy, *Brit. M. J.* **1**:969-971 (June 15) 1940.

supplemented with physical therapy in the treatment of these conditions. [ED. NOTE: The forms of treatment of spasmodic torticollis are still varied. Psychotherapy, physical therapy, immobilization in a plaster cast or a brace, drug therapy and operation have all produced good results in some cases. Each case must still be studied as an individual problem and treatment decided on accordingly.]

Occasionally torticollis is compensatory. This is exemplified in McCullough's ⁵⁰⁹ case, in which there was a spasm of unknown cause in the inferior oblique muscle of one eye. The patient, a child of 6, tilted the head to correct diplopia. Tenotomy of the muscle relieved both the diplopia and the torticollis.

Treatment of congenital torticollis is well covered by Soeur ⁵¹⁰ in a report of 20 cases, with excellent results in 19. He stresses correction of the contracture, minimum operative risk and avoidance of visible scars. For correction in patients under 14 years of age, both ends of the sternocleidomastoid muscle are severed. Local anesthesia is frequently employed. In bipolar tenotomy the author has found subcutaneous tenotomy of the clavicular attachment satisfactory; he advocates immobilization in a plaster cast for two months after operation. [ED. NOTE: The open method is still the procedure of choice. In many clinics the application of traction or of sand bags followed by early physical therapy is replacing the use of the plaster cast for postoperative immobilization.]

Injuries and Diseases of the Shoulder.—Nathanson ⁵¹¹ stresses the importance of complete physical examination of patients with pain in the shoulder. He reports 3 cases in which the symptoms in the shoulder with less careful examination might have been diagnosed as bursitis of the shoulder; further examination revealed a neoplasm in the pulmonary apex in 2 cases, and in the third case the patient was treated for bursitis with no relief. Later examination revealed an opaque lesion in the upper lobe of the right lung with erosion of the ribs. If such signs as Horner's syndrome are present or if after a reasonable trial treatment has given no relief, the patient should again be given a thorough physical examination.

McKenna ⁵¹² believes tendinitis, which may involve any or all the tendons, but principally affects those of the supraspinatus muscle and

509. McCullough, M. K.: Spasm of Inferior Oblique with Head Tilt, *Texas State J. Med.* **36**:507-510 (Nov.) 1940.

510. Soeur, R.: Treatment of Congenital Torticollis, *J. Bone & Joint Surg.* **22**:35-42 (Jan.) 1940.

511. Nathanson, L.: Pulmonary Apical Tumefaction Simulating Bursitis: Necessity for Routine Chest Examination for Patients with Shoulder Pain, *New York State J. Med.* **40**:860-864 (June 1) 1940.

512. McKenna, D. E.: Tendinitis of Shoulder, *M. Times, New York* **68**:259-263 (June) 1940.

long head of the biceps brachii muscle, is the primary lesion in most disabilities of the shoulder. He states that this is the result of excessive use, wear and tear, resulting in fibrillation, saponification and calcareous degeneration. The subacromial bursa is only secondarily involved.⁵¹³ Irrigation, as recommended by Patterson and Patterson,^{513a} is the accepted form of treatment for definite subacromial bursitis. In the presence of acute subacromial bursitis, especially with calcification, Bartels⁵¹⁴ feels that operation is necessary and that the calcareous deposit should be removed with a curet.

According to Kendrick,⁵¹⁵ periarthritis frequently follows subacromial bursitis as the result of trauma. When this occurs, rest in bed is often indicated, although needling or irrigation, as Weeks⁵¹⁶ also suggests, may give prompt relief from pain. Restoration of function should be the aim of all therapy. When the disease is quiescent and limitation is due to mature adhesions, with the patient under anesthesia the arm should be carefully brought into abduction and full elevation; then traction of 3 to 5 pounds (1.3 to 2.3 Kg.) should be applied to hold the arm in abduction and external rotation. This should be followed by physical therapy and active exercise; the arm should always be returned to a position of rest in full elevation and abduction until there is full passive motion without pain. This position can also be secured by slowly stretching with traction when manipulation is contraindicated. This treatment is the same as that suggested by McKenna.⁵¹²

After working with cadavers, Martin⁵¹⁷ makes an interesting statement about rupture of the supraspinatus muscle. He finds that the position of the humerus is the same whether the arm is carried into the upright position through the coronal or through the sagittal plane. Thus the humerus must rotate 180 degrees when the arm is elevated in the coronal plane. In this upright position the muscles inserted in the region of the bicipital sulcus are twisted around the surgical neck. It follows that if the arm is accidentally forced upward in the coronal plane while preventing lateral rotation of the humerus, one of four things happens: (1) The head of the humerus is dislocated; (2) the insertion of the tendon of the supraspinatus muscle is lacerated; (3) the acromial

513. (a) Patterson, R. L., Jr., and Patterson, R. H.: Further Observations on Treatment of Bursitis of the Shoulder, *Am. J. Surg.* **49**:403-408 (Sept.) 1940.
(b) McKenna.⁵¹²

514. Bartels, W. P.: Surgical Treatment of Acute Subacromial Bursitis, *J. Bone & Joint Surg.* **22**:120-121 (Jan.) 1940.

515. Kendrick, J. I.: Physical Therapy Principles of Periarthritis of Shoulder, *Arch. Phys. Therapy* **21**:41-44 (Jan.) 1940.

516. Weeks, A.: Subdeltoid Bursitis, *Arch. Surg.* **41**:554-556 (Aug.) 1940.

517. Martin, C. P.: Movements of Shoulder Joint with Special Reference to Rupture of Supraspinatus Tendon, *Am. J. Anat.* **66**:213-234 (March) 1940.

process is fractured, or (4) the greater tuberosity of the humerus is torn off. Lateral rotation is due partly to the action of the deltoid muscle, partly to the pull of the supraspinatus muscle and partly to the eccentric position of the coracoacromial arch.

The Nicola operation still seems to be the procedure of choice for recurrent dislocation of the shoulder, although Orell⁵¹⁸ has developed a technic in which a piece of os purum is implanted on the anterior rim of the glenoid cavity with a specially designed osteoperforator. According to Orell the operation is simple and can be performed quickly. Magnuson and Stack⁵¹⁹ report a familial incidence of recurrent dislocation of the shoulder; the condition was bilateral in twins and unilateral in their father, a brother and an uncle. [ED. NOTE: This is most unusual.]

Lieberman⁵²⁰ reports a case of the unusual condition of subluxation of the long head of the biceps from the bicipital groove. The patient was completely relieved of all symptoms by a Nicola operation.

Watson⁵²¹ reports a new technic for taking a superior view roentgenogram of the shoulder showing the end of the clavicle and the spine of the scapula. The patient stands erect with the right side to the film; the right arm is extended forward and the left arm at the side. The roentgen tube is at a distance of 6 feet (180 cm.) and is directed downward from above at an angle of 45 degrees. [ED. NOTE: A new technic for taking roentgenograms to show a different view of a joint is always welcome news to the surgeon.]

In cases of acromioclavicular dislocation, Murray⁵²² advocates the insertion of a Kirschner wire through the acromion into the clavicle. In the 5 cases he reports the results were excellent. The patients returned to work a few days after insertion of the wire. In 2 cases, wires were inserted from the coracoid process into the clavicle with equally good results. Removal of the wire is optional, since it produces no evidence of irritation. [ED. NOTE: The efficiency of this procedure is debatable. One of us (H. E. C.) has seen infection occur after this operation. It certainly should not be considered a routine procedure but should be used only in selected cases.]

518. Orell, S.: Surgical Treatment of Recurrent Dislocation of Shoulder Joint. *Surg., Gynec. & Obst.* **70**:945-947 (May) 1940.

519. Magnuson, P. B., and Stack, J. K.: Bilateral Habitual Dislocation of Shoulder in Twins: Familial Tendency, *J. A. M. A.* **114**:2103 (May 25) 1940.

520. Lieberman, H. S.: Traumatic Subluxation of Long Head of Biceps Brachii: Case Report, *J. Bone & Joint Surg.* **22**:425-428 (April) 1940.

521. Watson, W.: Abnormal View of Shoulder, *Radiography* **6**:76-77 (April) 1940.

522. Murray, G.: Fixation of Dislocations of Acromioclavicular Joint and Rupture of the Coracoclavicular Ligaments, *Canad. M. A. J.* **43**:270-271 (Sept.) 1940.

Rupture or tear of the long head of the biceps or of its radial attachment is rare except in the aged. Good results are reported by Kraus,⁵²³ Schrader⁵²⁴ and McKee⁵²⁵ from operative repair, which should always be the method of choice.

Bosworth⁵²⁶ reports most accurately the anatomic findings in 28 cases of chronic disability of the shoulder. He classifies these according to whether there is present: (1) no pathologic lesion, (2) a lesion of a tendon, (3) a bursal lesion or (4) an exostosis. He finds that an anterior incision in the deltoid muscle with division of the muscle fibers at the acromion gives an excellent exposure and leaves no functional defect. [ED. NOTE: This report should be carefully studied by all who perform operations on the shoulder.]

Cleaves⁵²⁷ reports a case of apophysitis of the acromion in which there was an irregular appearance similar to that found in the os calcis when it is affected by the same condition. It followed trauma. All symptoms subsided within a year.

Cervical Rib and Scalenus Anterior Muscle Syndrome.—Aynsworth⁵²⁸ has coined the term "cervicobrachial syndrome" for the mixed symptoms caused by cervical ribs and the scalenus anterior muscle. According to symptoms he divides the patients into three groups: (1) those who exhibit neurologic symptoms as their major manifestation; (2) those who exhibit vascular symptoms as their chief manifestation; (3) those who exhibit a combination of vascular and neurologic symptoms. Trauma⁵²⁹ is a precipitating cause in a high percentage of cases. As a rule symptoms are much more severe when there is an underlying cervical rib.^{529b} Smith⁵³⁰ reports a case in which there was a thickened

523. Kraus, H.: Traumatic Rupture of Biceps Tendon, *Beitr. z. klin. Chir.* **171**: 121-125, 1940.

524. Schrader, E.: Avulsion of Superior and Inferior Tendon Insertion of Biceps Brachii, *München. med. Wchnschr.* **87**:555-556 (May 24) 1940.

525. McKee, G. K.: Spontaneous Rupture of Tendon of Long Head of Biceps Brachii, *Brit. M. J.* **1**:1018 (June 22) 1940.

526. Bosworth, D.: Analysis of Twenty-Eight Consecutive Cases of Incapacitating Shoulder Lesions Radically Explored and Repaired, *J. Bone & Joint Surg.* **22**:369-392 (April) 1940.

527. Cleaves, E. N.: Unusual Shoulder Lesion (Osteochondritis of Scapular Acromial Apophyses), *J. Bone & Joint Surg.* **22**:182-184 (Jan.) 1940.

528. Aynsworth, K. H.: Cervicobrachial Syndrome: Discussion of Etiology with Report of Twenty Cases, *Ann. Surg.* **111**:724-742 (May) 1940.

529. (a) Jelsma, F.: Scalenus Anticus Syndrome—End Results of One Hundred Cases: Report of Five Illustrative Cases, *Internat. Clin.* **4**:219-225 (Dec.) 1940. (b) Donald, J. M., and Morton, B. F.: Scalenus Anticus Syndrome With and Without Cervical Rib, *Ann. Surg.* **111**:709-723 (May) 1940. (c) Aynsworth,⁵²⁸

530. Smith, B. C.: Thrombosis of Third Portion of Subclavian Artery Associated with Scalenus Anticus Syndrome, *Ann. Surg.* **111**:546-548 (April) 1940.

fascia lateral and posterior to the scalenus anterior muscle producing similar symptoms. For the milder forms palliative measures will suffice, but in most cases scalenotomy^{530a} or removal of the offending cervical rib⁵³¹ is the method of choice.

Kaplan⁵³² reports injections of 1 per cent solution of procaine hydrochloride into the scalenus anterior muscle giving relief that may be permanent. It is believed that the cervical sympathetic nerves through which the pain is mediated may be paralyzed. There is also a relaxation of the scalenus muscle.

Patterson⁵³³ considers aneurysm of the subclavian artery to be rare. He believes that in the scalenus muscle syndrome pressure is exerted during inspiration on the brachial plexus and the subclavian vessels and that circulatory disturbances are due to constant stimulations of the constrictor nerve fibers going to the artery but that in addition there may be direct pressure on the vessel.

Pain in the Cervical Portion of the Spine.—Neviaser⁵³⁴ reports a traction-manipulation treatment for stiff neck. It was used on 76 patients, with complete relief for 34, improvement for 19 and no relief for 3. The author recommends first heat and then massage for five minutes followed by heat for twenty minutes more. Traction is now applied by means of a head halter. The patient's heels barely touch the floor; the head is then rotated to stretch the contracted muscles. At the point of maximum rotation a click is often heard, and relief is frequently immediate. This procedure may be repeated the following day. For chronic stiffness of the neck, traction of the head with a 2 to 5 pound (0.9 to 2.3 Kg.) pull may be continued with the patient in bed. [ED. NOTE: This treatment may be dangerous if great care is not exercised in the control of stretching and rotation. It is certainly based on sound reasoning. How lasting the improvement is for this same group of patients and also the number of recurrences should be reported in two to five years.]

Retruded Chin.—In all cases of retracted chin, New and Erich⁵³⁵ state that there is a disturbance in the function of the jaws with abnormal

531. Silbert, S.: Complete Recovery from Serious Vascular Impairment Following Removal of Cervical Rib, *Surgery* 7:392-395 (March) 1940. MacFee, W. F.: Cervical Rib Causing Partial Occlusion and Aneurysm of Subclavian Artery, *Ann. Surg.* 111:549-553 (April) 1940.

532. Kaplan, L.: Painful Shoulder: Diagnosis and Treatment, *Pennsylvania M. J.* 44:289-297 (Dec.) 1940.

533. Patterson, R. H.: Cervical Ribs and Scalenus Muscle Syndrome, *Ann. Surg.* 111:531-545 (April) 1940.

534. Neviaser, J. S.: Traction Manipulation Treatment of "Stiff Neck," *M. Ann. District of Columbia* 9:75-77 and 108 (March) 1940.

535. New, G. B., and Erich, J. B.: Retruded Chins: Correction by Plastic Operation, *J. A. M. A.* 115:186-191 (July 20) 1940.

dental occlusion. The three types are: (1) retarded mandible due to malocclusion, (2) retruded mandible due to arrested growth in the lower jaw and (3) receding chin not associated with malocclusion. Orthodontic procedures will cure the condition in children if started early enough, but plastic procedures are required for adults. The authors recommend fitting costal cartilage over the symphysis of the mandible in all cases requiring operation. [ED. NOTE: This operation should be done only by a plastic surgeon or by one trained in such procedures.]

XVIII. CONDITIONS INVOLVING THE ELBOW, FOREARM, WRIST AND HAND

Lesion of the Elbow.—De Araujo⁵³⁶ revives interest in resection instead of amputation or simple drainage as treatment for suppurative and traumatic lesions of the elbow. The high percentage of resulting flail elbows does not discourage him. He describes an arthroplastic operation which succeeded in reestablishing stability in 1 case. Kini⁵³⁷ reports good results with the use of resection instead of arthroplasty in 9 cases of poorly reduced dislocation of the elbow. He was working in southern India, where his limited facilities made the more complicated operation precarious. [ED. NOTE: Current interest in vitallium must not be allowed to obscure the value of resection of the elbow in selected cases. Resection is still one of the best ways of solving the problem of chronic infection or mechanical derangement of the elbow.]

Burman⁵³⁸ describes a case in which débridement including resection resulted in a flail elbow. Stability and good function were obtained, and excessive valgus of the elbow was reduced by the insertion of strips of fascia, so placed as to imitate the ligamentum collaterale ulnare.

Slowick⁵³⁹ reports obtaining good results in 5 cases of epicondylitis of the humerus by injecting sodium morrhuate. Considerable reaction was obtained. A varying number of injections was used, in some cases one and in others three. The writer suggests that after preliminary injection of procaine hydrochloride 0.3 cc. of 5 per cent solution of sodium morrhuate, or even less, should be injected under the tendon of the extensor muscle. In the treatment of ganglions Ball⁵⁴⁰ injects

536. de Araujo, A.: Autoplastic Articular Reconstruction of the Unstable Elbow, *Rev. brasil. de orthop. e traumatol.* **2**:3-15 (Sept.-Oct.) 1940.

537. Kini, M. G.: Dislocation of Elbow and Its Complications: Simple Technique for Excision of Elbow, *J. Bone & Joint Surg.* **22**:107-117 (Jan.) 1940.

538. Burman, M. S.: Fascial Plastic Operation for the Restoration of the Ulnar Collateral Ligament of the Elbow in Marked Lateral Instability of the Joint After Its Resection, *Am. J. Surg.* **49**:112-115 (July) 1940.

539. Slowick, F. A.: Sodium Morrhuate in Treatment of Epicondylitis of the Humerus: Report of Five Cases, *New England J. Med.* **222**:1071-1074 (June 27) 1940.

540. Ball, E. J.: New Treatment of Ganglion, *Am. J. Surg.* **50**:722-723 (Dec.) 1940.

2 cc. or less of a proteolytic enzyme (carotid) to liquefy the gelatinous material, which can then be freely aspirated. After thirty minutes the enzyme tends to destroy the secretory action of the wall of the ganglion. After aspiration and irrigation with distilled water, a pressure dressing is applied. Recurrence is rare; but if it occurs, he suggests that a few drops of 10 per cent solution of sodium morrhuate be injected.

Lesions of the Forearm.—Boyd⁵⁴¹ describes a surgical approach to the proximal third of the radius and the ulna through one posterolateral incision. It has the virtue of exposing the upper third of the radius and, if necessary, all of the ulna without damaging the radial nerve. The incision is particularly suited to the open reduction of Monteggia's fracture.

Blount⁵⁴² advocates osteoclasis of both bones of the forearm to correct the deformity of resistant supination, which cannot be further corrected by other means and which occurs in children after poliomyelitis and obstetric injury to the shoulder. The cosmetic and functional results were good in 7 cases and fair in 2. In addition to avoiding a scar, the method has other advantages over osteotomy, in that the healing period is shorter and there is not the danger of nonunion that must be taken into account when open osteotomy is performed on children with subsequent disturbance of the position of the bone ends.

Volkman's Ischemic Contracture.—Rouhier and Bosson⁵⁴³ describe a case in which there were multiple fractures, including one just above the elbow. The latter was complicated by typical Volkmann ischemic contracture which terminated in gangrene of the forearm. This necessitated supracondylar amputation and afforded an opportunity for examination of the arm. Most of the gangrene was on the anteromedial surface of the forearm. Complete liquefaction of the muscles explained the relaxation of the flexion contracture after the first few days. Other muscles appeared healthy. Nerve trunks appeared normal on both macroscopic and microscopic examination. Careful dissection of the brachial artery and of its radial branch revealed no abnormality, and clinical examination of the proximal portion showed it to be normal. At the bifurcation there was a nonadherent clot the size of a large grain of wheat. Beyond the first centimeter into the hand, the ulnar artery was completely thrombosed. Veins were similarly thrombosed. The fracture had not affected the surrounding soft parts.

541. Boyd, H. B.: Surgical Exposure of Ulna and Proximal Third of Radius Through One Incision, *Surg., Gynec. & Obst.* **71**:86-88 (July) 1940.

542. Blount, W. P.: Osteoclasis for Supination Deformities in Children, *J. Bone & Joint Surg.* **22**:300-314 (April) 1940.

543. Rouhier, G., and Bosson, C.: Volkmann's Ischemic Paralysis Terminated by Gangrene and Amputation, *Mém. Acad. de chir.* **66**:409-415 (April 17-24) 1940.

Luzuy⁵⁴⁴ reports 2 cases in which Volkmann's ischemia in an early stage was present after a bullet wound in the forearm and in which the symptoms were relieved by injecting 5 or 6 cc. of a 0.5 per cent solution of procaine hydrochloride into the stellate ganglions. From his personal acquaintance with the work of Leriche, he concludes that in the absence of neural lesions proved by electric stimulation, Volkmann's contracture should be considered to have a vasomotor origin and should be treated by injecting procaine hydrochloride into the stellate ganglion.

Bruce⁵⁴⁵ records an instance of localized Volkmann contracture of the middle finger of the right hand following contusion of the volar aspect of the midforearm with a tennis ball. There was isolated involvement of the fibers of the flexor digitorum sublimis muscle to the middle finger. Open elongation of the involved tendon just above the transverse carpal ligament resulted in a "virtually complete restoration, both of appearance and of function."

Jones⁵⁴⁶ describes the pathologic changes noted in performing open reduction in a case in which Volkmann's contracture in a child 10 years old was in an early stage. He noted that the bellies of the muscles of the flexor group were blue-black with congestion. The involved fascia was divided. The lumen of the brachial artery was obliterated from 2 inches (5 cm.) above the elbow joint into the radial and ulnar branches. After removal of the tunica adventitia with its sympathetic nerve fibers there was no expansion of the artery in ten minutes, but complete return of circulation occurred later. The operation was performed four hours after the accident. Plewes⁵⁴⁷ reports a case to support his contention (to which Jones also subscribes) that the syndrome is produced by occlusion of arteries. The elbow of a girl of 7 was operated on one hour after a compound supracondylar fracture. Well developed Volkmann ischemia was already present. Débridement exposed the brachial artery, which "felt like a piece of string." No pulsation was felt in the radial or ulnar arteries. One inch (2.5 cm.) of the brachial artery was resected. The intima of the excised portion was discolored by subintimal hemorrhage, and there was a small thrombus attached to the wall. The median nerve was swollen and discolored. Five minutes after resection the hand was warm; a feeble radial pulse could be felt at the end of the operation.

544. Luzuy, M.: Ischemic Contractures from Traversing Bullet Wounds of Upper Extremities: Two Cases with Therapy by Procaine Hydrochloride Injection of Stellate Ganglion, *Mém. Acad. de chir.* 66:2-5 (Jan. 3-10) 1940.

545. Bruce, J.: Localized Volkmann's Contracture, *J. Bone & Joint Surg.* 22: 738-739 (July) 1940.

546. Jones, E. B.: Volkmann's Ischaemia: Observations at Open Operation, *Brit. M. J.* 1:1053-1054 (June 29) 1940.

547. Plewes, L. W.: Occlusion of the Brachial Artery and Volkmann's Ischaemic Contracture, *Brit. M. J.* 1:1054-1055 (June 29) 1940.

On the day after the operation there was complete median palsy which disappeared within three months. The writer concludes that early arteriectomy prevents the appearance of Volkmann's syndrome and cites 2 cases of Griffiths and 1 of Karusseau. It appears from the literature that after twenty-four hours arteriectomy will not prevent it.

Griffiths⁵⁴⁸ presents a masterly discussion of Volkmann's ischemic contracture which brings the subject up to date. In his opinion the syndrome is due to injury of arteries and to accompanying spasm of the collateral circulation. The intravenous use of papaverine is suggested. If this fails, the contused or lacerated portion of the artery should be excised between ligatures.

Surgical Approach to the Wrist Joint.—Smith-Petersen⁵⁴⁹ presents a new surgical approach to the wrist joint which is particularly useful in arthrodesing the radiocarpal joint without interfering with pronation and supination. The incision may be extended distally to expose the row of carpal bones.

The incision starts two and one-half inches above the ulnar styloid running parallel with the ulna to a point just distal to the styloid; it then curves anteriorly in the direction of the proximal end of the fifth metacarpal; the distal portion runs parallel with this bone for a distance of approximately one inch. A bayonet incision of this type results in two flaps, which are easily retracted. Since the incision is over the ulnar aspect of the wrist, the resulting scar is out of sight most of the time.

By a division of the subcutaneous fat and fascia, the ulnar periosteum is exposed and incised. If the surgeon is not in too much of a hurry, a true subperiosteal exposure of the ulna can be obtained.

Following an oblique osteotomy, the distal inch or so of the ulna is removed, exposing the ulnar aspect of the radius. The capsule and the ligaments are reflected from the radius along with the periosteum of the latter, exposing the radiocarpal joint. The same procedure is carried out distally, reflecting capsule and ligaments from the carpus. The increased mobility thus obtained facilitates the complete removal of the cartilage from the radius and the carpus. With the hand in the optimum position of dorsiflexion, slots are cut in the radius and the carpus, into which the graft is sunk. As a rule, the excised portion of the ulna, properly shaped, makes an efficient graft; the remaining fragments are packed around the volar aspect of the graft.

Anatomy of the Wrist.—Salsbury⁵⁵⁰ presents a detailed anatomic study of the ulnar bursa based on the dissection of 46 hands. He is particularly interested in the communication between the ulnar bursa and the digital sheath of the little finger. In 25 per cent of the hands there was no communication; in 50 per cent the communication was

548. Griffiths, D. L.: Volkmann's Ischaemic Contracture (Hunterian Lecture), *Brit. J. Surg.* **28**:239-260 (Oct.) 1940.

549. Smith-Petersen, M. N.: New Approach to Wrist Joint, *J. Bone & Joint Surg.* **22**:122-124 (Jan.) 1940.

550. Salsbury, C. R.: Contribution to the Anatomy of the Ulnar Bursa, *Canad. M. A. J.* **43**:430-432 (Nov.) 1940.

small and valvelike. In most of the hands without normal communication the two synovial sacs were separated by only a thin septum. He suggests that the pressure of an infected mass could easily rupture this septum and that this would explain the high percentage of cases in which the communication is recorded. He thinks that infections of the ulnar bursa are likely to reach the digital sheath but that infections of the digital sheath are less likely to spread to the bursa, because of the valvelike arrangement of the ulnar bursa.

Cave⁵⁵¹ discusses the carpus from the developmental and anatomic points of view with special reference to fractures of the scaphoid bone. He reviews the development and blood supply of the carpus. A fracture through the midportion of the bone frequently involves the bifurcation of the main nutrient artery, interrupting the blood supply of the proximal fragment. The distal fragment is nourished by a smaller artery entering the tubercle. The loss of nutrition is an important factor in the production of nonunion in some cases. Cave emphasizes the importance of anteroposterior roentgenograms with the hands in ulnar deviation and oblique views with the hands in midpronation in the diagnosis of this fracture. In a series of 110 injuries of the carpus, fracture of the scaphoid bone occurred 68 times, usually as the result of acute dorsiflexion of the wrist. For fresh fracture he advocates the conventional immobilization of the thumb in a cast with the wrist in 30 degrees of dorsiflexion and 15 degrees of radial deviation until union is roentgenologically demonstrable. Prolonged immobilization is more important than physical therapy, and he suggests the use of a leather wristlet after removal of the cast. Definite roentgen evidence of nonunion after four months is an indication for operative treatment. The writer recommends either a slot or a dowel graft. The technic of the dowel-grafting operation is given as used in the later cases.

Kienböck's Disease.—Erler⁵⁵² recommends drilling the affected lunate bone with a 2 mm. spiral drill, which serves to remove some of the necrotic tissue. Prolonged rest is also necessary. Simonetti⁵⁵³ describes the development of necrosis of the lunate bone in a case in which the wrist was subjected to repeated minor traumas. He suggests the designation of two phases of the malady. In the first there is a roentgenologic picture of nonspecific osseous rarefaction. In the second there is osteosclerosis. He emphasizes the importance of the circulatory factor in causation.

551. Cave, E. F.: Carpus, with Reference to Fractured Navicular Bone, *Arch. Surg.* **40**:54-76 (Jan.) 1940.

552. Erler, F.: Therapy of Kienböck's Disease, *Ztschr. f. Orthop.* **70**:357-360, 1940.

553. Simonetti, C.: Kienböck's Disease: Review of Literature and Report of Case, *Ann. di radiol. diag.* **14**:59-67 (Feb.) 1940.

Etcheverry⁵⁵⁴ reviews the literature and reports 2 cases. He injects the arterial tree of the wrist of an infant to demonstrate the extension of the branches to the scaphoid and semilunar bones. Almost the entire blood supply enters the semilunar bone on the dorsum of the wrist, the site of most trauma. The semilunar bone contains end arteries which cannot be easily replaced if damaged. There are no muscle attachments to act as avenues of entrance for new vessels. Repeated minor traumas are the most likely cause of Kienböck's disease. Caby⁵⁵⁵ records the occurrence of bilateral osteoporosis of the carpus with Kienböck's disease in a case of bilateral cervical rib. He feels that the vasomotor syndrome associated with the cervical ribs was more than coincidental in causing the osseous changes.

Loose Body in the Wrist Joint.—A woman 45 years old complained to Michaelis⁵⁵⁶ of recurrent attacks of numbness, locking, pain and swelling in the ulnar half of the left wrist. The symptoms were relieved by change of position. Roentgen examination revealed no abnormalities. Operation showed a cartilaginous free body 15 mm. long in the wrist joint. Removal was followed by complete recovery.

Madelung's Deformity.—Horwitz⁵⁵⁷ was stimulated by operation on a patient with Madelung's deformity to a detailed anatomic and roentgen study of the wrist joint. After operation he achieved stability in the relaxed and snapping wrist joint by threading half the tendon of the extensor carpi radialis brevis muscle through holes drilled in the distal end of the radius and the lunate bone. The result at the end of six months was good. Marti⁵⁵⁸ reviews the entire subject of Madelung's deformity and concludes that the condition results from a combination of congenital predisposition, endocrine factors at puberty and repeated minor traumas. He feels that surgical intervention is seldom indicated and that progression of the lesion may be prevented by support.

Marottoli and Brocca⁵⁵⁹ obtained stability and good range of motion in 1 case of traumatic dorsal subluxation of the distal end of the ulna

554. Etcheverry, A. J.: Study of Two Cases of Kienböck's Disease, *Med. españ.* **3**:220-226 (March) 1940.

555. Caby: Bilateral Cervical Rib with Osseous Rarefaction, and Kienböck's Disease of Both Arms, *Mém. Acad. de chir.* **66**:232-235 (Feb. 28-March 6) 1940.

556. Michaelis, L. S.: Locking Wrist, *Lancet* **2**:229-230 (Aug. 24) 1940.

557. Horwitz, M. T.: Anatomic and Roentgenologic Study of Wrist Joint: Observations on Case of Recurrent Radio-Carpal Dislocation Complicating Madelung's Deformity and Its Surgical Correction, *Surgery* **7**:773-783 (May) 1940.

558. Marti, T.: Madelung-Dupuytren's Disease with Report of Case, *Rev. méd. de la Suisse Rom.* **60**:31-50 (Jan. 25) 1940.

559. Marottoli, O. R., and Brocca, M.: Fibrocartilaginous Lesions of Inferior Radiocubital Joint, *An. de cir.* **6**:79-84 (March) 1940.

by extirpating the fibrocartilage, reconstructing the radioulnar ligament and encircling the ulna with stout linen.

Roentgen Examination of the Carpus.—Graziani⁵⁶⁰ analyzes the routine roentgen examination of the carpus and points out that many important details are missed. He proposes modification of the technic and suggests sixteen possible views for the exhaustive study of the wrist. These comprise: a dorsopalmar view with the wrist straight and with the wrist in radial and in ulnar deviation; a palmodorsal view with the wrist in the same three positions; a radioulnar view with the wrist straight and with it in flexion and extension; an ulnoradial view with the wrist the same in three positions; two radioulnar oblique views and two ulnoradial oblique views. In particular these projections were effective as follows:

1. In both the dorsopalmar and the palmodorsal view with the hand in ulnar deviation there is shown a full profile of the scaphoid without overlapping of the carpal bones at the distal third.
2. In the palmodorsal view, superimposition of the capitate and hamate bones is avoided, and the articulations of the two bones are clearly shown.
3. In the palmodorsal position with ulnar deviation there is good visualization of the articulation between the hamate and the triquetrum bones and of the partial dissociation of the pisiform and triquetrum bones.
4. In the palmodorsal view an anteroposterior aspect of the styloid process of the ulna is shown; in the dorsopalmar view the profile is shown.
5. The best visualization of the pisiform bone is obtained in the ulnoradial view with the wrist straight.
6. The ulnoradial view with the hand flexed offers the best visualization of the scaphoid bone in the distal half and of the articulations of the scaphoid with the greater multangular bone.
7. With the hand in hyperextension, both the radioulnar and ulnoradial view show the articulation of the capitate and semilunar bones.
8. With the hand in hyperextension, the ulnoradial view shows well the greater and lesser multangular bones.
9. The best visualization of the greater and lesser multangular bones is obtained in the oblique dorsoradial view.
10. The oblique dorsoulnar view is best for an accurate profile of the carpal bones. [Ed. NOTE: This is the routine view commonly employed for demonstrating fracture of the middle of the scaphoid bone which may not be visible in any other view.]

560. Graziani, A.: Roentgenological Study of the Wrist, *Radiol. med.* 27: 382-392 (May) 1940.

Anatomy of the Hand.—The detailed anatomy of the midpalmar compartment is thoroughly described by Anson and Ashley.⁵⁶¹ On the basis of numerous dissections they describe and beautifully illustrate the compartment with the associated spaces and limiting layers. They conclude that the thenar space of Kanavel "lies between the lateral septum and the adductor pollicis fascia." The midpalmar space "is merely a bilaminar arrangement, whereby the floor of the fascial lining of the midpalmar compartment is locally split over the region of the last three metacarpal bones." They summarize their findings by saying

that the regular, simple stratification is altered—and rendered complex—in the hand by interposition of the long flexor tendons of anti-brachial origin; in producing a specialized sheath for these structures a bilaminar tube results, fastened by aponeurotic septa to skin and to bones, itself divides into compartments for its contents. Branches of arciform arteries, superficial and deep to the sheath, communicate through anastomotic stems which use the intravaginal septa as their means of transmission.

The clinical need for such anatomic knowledge in the treatment of infections is well illustrated by Pemberton.⁵⁶²

Dupuytren's Contracture.—Hancock⁵⁶³ suggests that Dupuytren's contracture is not a definite entity but that the local manifestation of a metabolic disturbance, such as gout, rheumatism, focal infection or trauma, may be a contributing cause. Griswald, in discussing Hancock's paper, reports a case in which a nodule proved to be a neurofibroma and was removed from the palm of an otherwise normal hand; a typical Dupuytren contracture later developed.

Meyerding⁵⁶⁴ cites examples from 315 patients with Dupuytren's contracture, of whom he operated on more than 100, to illustrate the advantage of complete excision of the palmar fascia followed by splinting and physical therapy. He noted the frequent occurrence in the early stages of local soreness or redness of the palm. A similar phenomenon has appeared postoperatively in the absence of infection. He believes that "repeated trauma may be a possible exciting factor in the causation of the contracture," but he suggests also "removal of foci of infection and improvement of the general health" in the interest of prevention of the disease. Variability in the rate of progress is remarkable. Meyerding records occasional arrest for years of the progress of the deformity.

561. Anson, B. J., and Ashley, F. L.: Midpalmar Compartment, Associated Spaces and Limiting Layers, *Anat. Rec.* **78**:389-407 (Nov. 25) 1940.

562. Pemberton, P. A.: Infection of the Fascial Spaces of the Palm, *Am. J. Surg.* **50**:512-515 (Dec.) 1940.

563. Hancock, J. D.: Dupuytren's Contracture, *Kentucky M. J.* **38**:290-293 (July) 1940.

564. Meyerding, H. W.: Treatment of Dupuytren's Contracture, *Am. J. Surg.* **49**:94-103 (July) 1940.

König⁵⁶⁵ agrees with the prevalent opinion that the lesion is caused by constitutional and hereditary factors. Pathologic studies show hyperplasia in the initial stage and contracture in a late stage.

Ferrarini⁵⁶⁶ is unique among authors in debating the significance of the contracture as an occupational disease. He notes that there is no established precedent or even consideration of the problem in the Italian statutes, and he finds little help in the reports from other countries. He collects at great length and classifies all available opinions; his work represents a monumental task of combing the literature. However, he offers nothing new and concludes that while there is no proof of the causal relation of trauma, proof of a constitutional factor or individual predisposition is equally difficult from a legal or insurance standpoint.

Snapping Fingers.—From a study of 20 cases of congenital contracture of the thumb, Beck⁵⁶⁷ concludes that the deformity is always tendinous. Dermatogenous and myogenous contractures are traumatic. In the 20 cases studied there were hard nodules in the tendons of the flexor muscles, but none of the thumbs snapped. In 1 there was an associated fourth finger that did. Pathologic changes consisted of a nodular enlargement of the tendon just proximal to a hard thickening of the sheath. When the sheath was only divided, the recovery was incomplete in most cases; but when the hard area was excised, the recovery was complete. The pathologic changes seemed to be degenerative. The author concludes that congenital contracture of the thumb is a hereditary deformity which is a recessive characteristic and more prevalent in women than in men. He advises operation because conservative treatment rarely gives satisfactory results. He cites Jahss⁵⁶⁸ in support of this opinion. [ED. NOTE: In the article cited Jahss said, "There is only one treatment and that is surgical." In a personal communication to one of us (W. P. B.) he added that he had never tried conservative treatment. Jahss distinguishes between trigger finger and congenital contracture. Either condition is more distressing to the mother than it is to the child. Simple contracture will invariably yield to conservative treatment, such as splinting and gentle manipulation. In a series of 6 cases of trigger thumb in infants all the patients recovered completely after treatment by splinting. In 1 case there was recurrence after removal of the splint, but the patient recovered spontaneously with-

565. König, E.: Dupuytren's Contracture, *Med. Klin.* **36**:568-571 (May 24) 1940.

566. Ferrarini, M.: Dupuytren's Contracture Can Be Considered as Occupational Disease, *Rassegna di med. indust.* **11**:70-97 (Feb.) 1940.

567. Beck, W.: Congenital Contracture of the Thumb, *Arch. f. orthop. u. Unfall-Chir.* **40**:318-325, 1940.

568. Jahss, S. A.: Trigger Finger in Children, *J. A. M. A.* **107**:1463-1464 (Oct. 31) 1936.

out further treatment. There is no more justification for the operative treatment of this condition in an infant than there is for open reduction of a fracture of the distal end of the radius in a child.]

Schörcher⁵⁶⁹ reports a case in which the patient was a 25 year old woman with traumatic rupture of the radial strand of the tendon of the flexor digitorum sublimis muscle; the lesion gave rise to a snapping finger of unusual origin. The enlargement of the tendon was found to snap at operation. Spisic⁵⁷⁰ was impressed by the disability entailed by snapping of his own fifth finger. He had to undergo operative treatment before he could comfortably and efficiently continue his surgical practice.

Operations on the Fingers.—Burman⁵⁷¹ reports using a vitallium thimble in two arthroplasties on interphalangeal joints. The results were most encouraging.

Kaplan⁵⁷² suggests the need for operation to reduce the typical mallet or baseball finger. In his opinion the original deformity is frequently due to displacement of the joint rather than to avulsion of the attachment of the tendon. Usually the cause is a rupture of the tendon of the extensor muscle or a fracture of the base of the terminal phalanx. For rupture of the tendon, he urges operation; for fracture he feels that the results will be improved by open operation.

Jelsma⁵⁷³ suggests the use of ordinary collodion to maintain extension of the distal interphalangeal joint of a finger. He severed the extensor tendon of his own index finger. After the wound had healed, he was able to operate when collodion was painted on the distal two phalanges with the distal joint in extension. He felt that the constricting effect of collodion was desirable.

Injury of the Digits.—Schoolfield⁵⁷⁴ enters a plea for early recognition of and prompt attention to injuries of the first carpometacarpal joint with rupture or overstretching of the capsule but without injury to the bone. Dorsal dislocation of the base of the first metacarpal bone usually leads to relaxation of the capsule if immobilization with traction

569. Schörcher, F.: Snapping Finger Due to Injury to the Tendons, *Zentralbl. f. Chir.* **67**:627-628 (April 6) 1940.

570. Spisic, B.: The Trigger Finger, *Zentralbl. f. Chir.* **67**:157-159 (Jan. 27) 1940.

571. Burman, M. S.: Vitallium Cap Arthroplasty of Metacarpophalangeal and Interphalangeal Joints of Fingers, *Bull. Hosp. Joint Dis.* **1**:79-89 (Oct.) 1940.

572. Kaplan, E. B.: Mallet or Baseball Finger, *Surgery* **7**:784-791 (May) 1940.

573. Jelsma, F.: Finger Splint That Will Not Impair Hand Function, *Am. J. Surg.* **50**:571-572 (Dec.) 1940.

574. Schoolfield, B. L.: Injuries About Carpometacarpal Joint of Thumb, *South. M. J.* **33**:354-355 (April) 1940.

is not promptly applied. When the relaxation becomes chronic, the author suggests surgical closure of the tear and plication of the capsule. Nutter⁵⁷⁵ emphasizes the need for traction and rotation to free the sesamoid bones and reduce them to their normal position when digital sesamoid bones are caught in a dislocation of the joint of a phalanx. He reports 2 cases, in one of which open reduction was necessary; in the other closed reduction was done by preliminary traction and rotation and then manipulation of the ends of the bones.

Williams⁵⁷⁶ reports 3 cases in which hysteria was associated with marked edema in the hand and the forearm. The swelling was attributed to associated dependency and immobility. The edema disappeared with elevation. In 1 case there was permanent damage with extension contractures of the fingers after eighteen months of swelling. Three experiments were performed to show the effect of dependency and immobility on the hand. [ED. NOTE: There is no record of careful investigation to rule out self-imposed constriction near the elbow as a factor in the production of edema, although this was probably considered by the author.]

XIX. TECHNIC, AMPUTATIONS AND APPARATUS

New or Improved Operations.—Hatt⁵⁷⁷ reports using for seven years a technic of central bone grafting for arthrodesis of the knee which has facilitated that none too easy procedure and has been associated with no unfortunate complications or retardation in growth, even though the tibial graft passes completely through both epiphysial lines adjacent to the joint. An analogous technic has also been used advantageously on the ankle. [ED. NOTE: The fact that retardation of growth has not occurred in these cases confirms the belief of one of us (J. W. W.) that curettage or cauterization of the metaphysial plate in using White's modification of Phemister's technic of epiphysiodesis is unnecessary.]

Encountering the usual difficulty in passing the long head of the biceps muscle through the bone tunnel in the Nicola operation, Baker⁵⁷⁸ employs a piece of Dakin's tubing 3 mm. in its inside diameter, 1 mm. thick and 15 cm. long as a tendon carrier. The tubing, the opening of which has been dilated by a hemostat, is slipped over the end of the tendon after the stay suture in the proximal portion of the tendon has been passed through the tube. A silver wire hairpin is then passed

575. Nutter, P. D.: Interposition of Sesamoids in Metacarpophalangeal Dislocations, *J. Bone & Joint Surg.* **22**:730-734 (July) 1940.

576. Williams, C.: Hysterical Edema of Hand and Forearm, *Ann. Surg.* **111**: 1056-1064 (June) 1940.

577. Hatt, R. N.: Central Bone Graft in Joint Arthrodesis, *J. Bone & Joint Surg.* **22**:393-402 (April) 1940.

578. Baker, L. D.: Nicola Operation: Simplified Technique, *J. Bone & Joint Surg.* **22**:118-119 (Jan.) 1940.

through the bone tunnel, and the tubing is pulled through and is followed by the tendon. Baker values highly the soft, flexible silver wire loop which simplifies pulling the tubing and tendon through the tunnel. [ED. NOTE: One of us (J. W. W.) has simplified this technic by cutting a deep trench in the head, slipping the uncut tendon into it and replacing the excised piece.]

Harmon and Krigsten⁵⁷⁹ discuss rather extensively the problem of legs of unequal length and report a somewhat limited experience with various corrective procedures. They mention that undercorrection rather than overcorrection has been the most frequent error. They mention the unsuitability of shortening the legs of children; to a lesser degree the same holds true for adults. On the other hand, they state that lengthening should be done only by experienced surgeons with adequate equipment and suitable surroundings. [ED. NOTE: This is an article well worth reading in full.]

Operations on Tendons.—Once more Bunnell⁵⁸⁰ presents results of his wide experience with operations on tendons. He gives more rule of thumb advice, stating that primary repair of tendons should not be done except when the indications of time, condition of the wound, hospital facilities and special training of surgeons augur well. If conditions are not propitious, it is better to postpone repair of tendons until later and simply débride, close the wound loosely but securely and cover vulnerable parts. A delay of six months at least should be allowed if bone infection has complicated healing. If extensive operation is done at the time of the injury and sepsis follows, the subsequent procedures are much more difficult to perform and less likely to be successful. Performing repair of tendons when a sheath does not exist is most difficult and adds considerably to the probability of failure. Trauma must be reduced to a minimum, and a simple nonirritating stitch must be employed on the tendon. Bunnell recommends using a fine stainless steel wire and describes the manner of its insertion and removal. [ED. NOTE: This is another valuable contribution from a master surgeon in this field.]

Koch⁵⁸¹ in an article on the surgical principles of repair of divided nerves and tendons condemns the use of antiseptics in open wounds. He urges gentleness in handling the tissues and the use of soft sterile cotton and soapsuds for cleansing the wound instead of green soap and gauze. The soapsuds should be washed away with sterile water. This

579. Harmon, P. H., and Krigsten, W. M.: *Surgical Treatment of Unequal Leg Length*, Surg., Gynec. & Obst. **71**:482-490 (Oct.) 1940.

580. Bunnell, S.: *Primary Repair of Severed Tendons: Use of Stainless Steel Wire*, Am. J. Surg. **47**:502-516 (Feb.) 1940.

581. Koch, S. L.: *Some Surgical Principles in Repair of Divided Nerves and Tendons*, Quart. Bull. Northwestern Univ. M. School **14**:1-8, 1940.

should always be done with the patient under general anesthesia. The cuff of a sphygmomanometer should be used rather than an ordinary tourniquet. For the repair of tendons he recommends dry, unwaxed fine silk. The use of drains is discouraged. [Ed. NOTE: This is a good article, well written and worthy of further study.]

Mason⁵⁵² describes the details of the technic of repairing tendons. He quotes Bunnell and joins with Koch in advising against the use of antiseptics. He, too, recommends soft cotton instead of gauze. Longitudinal incisions in the hand must be avoided whenever possible, because of the tendency of all scars to longitudinal contraction, particularly on the palmar surface. He also describes his favorite stitch for repairing tendons and advises making a window in the tendon sheath over a repair to avoid as much as possible the formation of adhesions. He is not so positive as Bunnell about the need of immediate repair.

New Surgical Instruments.—The continuance in popularity of the use of metals and alloys which resist corrosion and are nonirritating to tissue has resulted in the development of new surgical procedures. To facilitate the performance of these procedures, instruments are being devised which otherwise would never have been considered necessary.

The so-called vitallium cup arthroplasty of the hip of Smith-Petersen stimulated Norton⁵⁵³ to devise an adjustable reamer for rounding the head of the femur to take the place of a battery of expensive handmade instruments. [Ed. NOTE: One of us (J. W. W.) has watched Smith-Petersen use this instrument, and although the latter prefers the original solid cup-shaped reamers, he approves the adaptable reamer and recommends its use.] It has four adjustable cutting leaves which facilitate the actual procedure and reduce the time element in shaping the head. Because of difficulty in manufacture it is expensive; it is hoped that its cost can be reduced as it is made in larger quantities.

The return to greater popularity of internal fixation screws caused Tenopyr and Corriero⁵⁵⁴ to devise what is erroneously called a jig for holding screws of various sizes together with their appropriate taps and drill points before their insertion into bone. With this holder one can see at a glance whether an adequate assortment of screws is available for an elected procedure. A new screwhead described by these authors differs from the usual slotted head; in a blank top surface a hexagonal hole has been made to receive a hexagonal wrench. The absence of the

552. Mason, M. L.: Primary and Secondary Tendon Suture: Discussion of Significance of Technique in Tendon Surgery, *Surg., Gynec. & Obst.* **70**:392-402 (Feb., no. 2A) 1940.

553. Norton, P. L.: Adjustable Reamer for Use in Arthroplasty of Hip, *J. Bone & Joint Surg.* **22**:458-459 (April) 1940.

554. Tenopyr, J., and Corriero, W. P.: Use of Tool Jig and New Type of Screw in Bone Plating, *Am. J. Surg.* **48**:475-476 (May) 1940.

slot helps to reduce the trauma associated with insertion of the screw, since slots tend to catch and tear soft tissue in the wounds. The use of the long hexagonal wrench, which fits snugly, facilitates insertion and largely eliminates the need for a screw-holding screw driver. Several improved designs of the latter have been put on the market but have not yet been described in the literature.

Surgeons who have had difficulty in securing adequate illumination of the interior of knees when performing arthrotomy will be glad to know of a self-illuminating retractor for the patella modeled by Cobey⁵⁸⁵ after the Bennett steel retractor. Its chief handicap is that heat sterilization is not practicable for lucite, of which its retracting end is made, and cold chemical sterilization is required.

Best⁵⁸⁶ describes an instrument devised to prevent a drill point from slipping off narrow rounded bones. [ED. NOTE: This appears to be a simple ingenious device, but one wonders whether there is any need for it. A sharp drill and an ordinary center punch usually suffice.]

Macey⁵⁸⁷ has devised a new instrument for passing portions of tendon and fascia lata through long tunnels. It consists of a metal sleeve $\frac{3}{16}$ inch (0.48 cm.) in length. When it is forced down over a small pair of forceps, the teeth of which grip the end of a tendon, it holds the latter securely until it is released after being brought through the tunnel. [ED. NOTE: It seems that this would be more useful if it could be constructed so as to be flexible, particularly for work around the ankle.]

A distracting bone-holding apparatus somewhat on the order of the Anderson anatomic splint has been designed by Haboush,⁵⁸⁸ who claims that better control of the fractured end of a bone can be obtained by two pins through both fragments, one pin being located near the fracture site. [ED. NOTE: The illustration of the apparatus gives the impression that it would be rather expensive, and one wonders whether the added risk of establishing direct communication into the fracture cavity with a pin so near it is justified by the questionable advantage of better control. It looks like a dangerous instrument in the hands of an inexperienced surgeon, and one feels that an experienced surgeon would devise some less hazardous method to accomplish his aims.]

585. Cobey, M. C.: Self-Illuminating Patella Retractor, *J. Bone & Joint Surg.* **22**:1103 (Oct.) 1940.

586. Best, F.: New Instrument for Fixation of Drill, *Zentralbl. f. Chir.* **67**: 147 (Jan. 27) 1940.

587. Macey, H. B.: New Instrument for Passing Portions of Tendons and Fasciae Latae, *Am. J. Surg.* **47**:686 (March) 1940.

588. Haboush, E. J.: Principles Governing Treatment of Fractures and Bone Lengthening by Direct Skeletal Means and New Apparatus: Preliminary Report, *Surgery* **7**:356-363 (March) 1940.

For those surgeons who prefer the subcutaneous drilling of ununited fractures a guide has been devised by Shifrin⁵⁸⁹ which permits the insertion of a drill into bone through a small $\frac{1}{4}$ inch (0.64 cm.) incision in the skin. It is large enough to take a $\frac{3}{32}$ inch (0.24 cm.) drill point and has three sharp prongs beveled from the inside; it engages the bone and aids in getting the drill started. The instrument consists of a tempered steel tube $1\frac{1}{2}$ inches (3.8 cm.) or more long, depending on the depth of the bone beneath the skin; a handle is attached to the tube at right angles. The guide can be easily directed so that holes may be drilled in any desired direction with great ease, since the bone is steadied by the prong-point guide.

Using the same principle employed in the White Smith-Petersen nail extension and extractor, Cahan⁵⁹⁰ has devised a Moore-pin extractor which can be securely attached to the pin that is to be removed.

Overholt,⁵⁹¹ a thoracic surgeon, has devised a self-retaining scapula retractor, the idea of which might be employed in orthopedic operations in which surgical assistants are few or space for them at the operating table is lacking for one reason or another. The principle on which the apparatus depends is the employment of a rigid support entirely outside the operating field to which a sterile retractor, clamp or forceps might be attached, the latter being in the field of operation. One instance in which such a device might be of value is holding together tendons which are being united. [ED. NOTE: Too many hands in a small field impede the operator, and yet in such instances traction in just the right place and in the required amount is most desirable. In this apparatus a reel and chain are the traction elements employed, but one of us (J. W. W.) suggests rubber bands as more adaptable and simpler.]

Metallic Internal Fixation.—Vitallium for internal fixation still seems to hold the stage, although a few authors have voiced the opinion that other alloys, particularly stainless steel, are practically as good and have the advantage of more strength. Among those who advocate the use of vitallium are Stuart,⁵⁹² Tuell,⁵⁹³ Cameron⁵⁹⁴ and Secord and

589. Shifrin, P. G.: Guide for Drilling Ununited Fractures, J. Bone & Joint Surg. **22**:1101-1102 (Oct.) 1940.

590. Cahan, A. M.: Cahan Nail Extractor, Am. J. Surg. **50**:140-141 (Oct.) 1940.

591. Overholt, R. H.: Self-Retaining Scapula Retractor, J. Thoracic Surg. **9**: 291-293 (Feb.) 1940.

592. Stuart, F. A.: Use of Vitallium Screws in Fractures of Long Bones, J. Oklahoma M. A. **33**:8-11 (May) 1940.

593. Tuell, J. I.: Vitallium in Internal Fixation in Bone Surgery, Northwest Med. **39**:163-165 (May) 1940.

594. Cameron, D. M.: Vitallium in Bone Surgery with Particular Reference to Its Clinical Irritability, Proc. Staff Meet., Mayo Clin. **15**:561-564 (Sept. 4) 1940.

Breck.⁵⁹⁵ The latter, because of the difficulty of removal, recommend that all vitallium be left permanently in place, assuming its complete inertness. Burke⁵⁹⁶ in comparing the corrosive effect of various metals in tissues urges the use of a rare metal, tantalum, claiming that it "is comparable to steel in its strength, toughness and workability." This metal is not an alloy, and its behavior, if pure, is thus more dependable. No idea as to its cost or source is given. [ED. NOTE: This metal is not yet available for general use.]

Hudack⁵⁹⁷ recommends a high chromium, low nickel steel alloy when certain requirements are fulfilled; it should be polished and "passivated by immersion in 20 per cent nitric acid at 65 C. for a half hour to give, theoretically, a molecular chromic oxide coating." Detailed and complicated instruction is given on how to reduce further the electrolytic corrosive action. [ED. NOTE: The latter might tend to deter one from using this alloy if he did not appreciate that all material to be left in tissue should be more or less passivated.]

Bothe, Beaton and Davenport⁵⁹⁸ report a series of experiments with animals in which various metals as well as two alloys were embedded in bone. It was found that pure manganese promoted the production of much callus and that titanium was as well tolerated as vitallium and stainless steel. [ED. NOTE: The formula is not given.] They are of the opinion that reaction of living tissue, particularly bone, is a chemical rather than an electric phenomenon. The physical properties of manganese do not permit its use as a metal. They call attention to the value of titanium, lamenting that metallurgists have not yet found a way to work it.

The use of the vitallium wood type screw instead of the Sherman type is advocated by Stuart.⁵⁹² However, only a small series of cases is reported. [ED. NOTE: The conclusions may be premature, at least about the design of the screws.] This author recommends the use of vitallium for internal fixation. [ED. NOTE: In the opinion of one of us (J. W. W.) the ideal material has not yet been found, and it is his belief that in the not too distant future, possibly as the result of efforts associated with the present war, a more satisfactory agent, whether pure

595. Second, E. W., and Breck, L. W.: Report of Case in Which Vitallium Plate Could Not Be Removed, *J. Bone & Joint Surg.* **22**:749 (July) 1940.

596. Burke, G. L.: Corrosion of Metals in Tissue and Introduction to Tantalum, *Canad. M. A. J.* **43**:125-128 (Aug.) 1940.

597. Hudack, S.: High Chromium: Low Nickel Steel in Operative Fixation of Fractures, *Arch. Surg.* **40**:867-884 (May) 1940.

598. Bothe, R. T.; Beaton, L. C., and Davenport, H. A.: Reaction of Bone to Multiple Metallic Implants, *Surg., Gynec. & Obst.* **71**:598-602 (Nov.) 1940.

metal or alloy, will be discovered. It is becoming more evident that while vitallium appears to be the most inert material its brittleness and lack of strength in general subtraet from its usefulness to a considerable extent. When strong internal fixation material is needed the better type of stainless steel seems to be most popular, that is, the so-called 18 to 8 alloy.]

Amputations.—The Council on Physical Therapy of the American Medical Association published three chapters of a proposed Handbook on Amputations in the latter part of 1940, all of which were written for and are helpful to the occasional amputator, as most surgeons fortunately are. The first chapter,⁵⁹⁹ which treats of psychologic and physiologic principles in amputations, is the least practical; the use of cineplastic technic is discouraged because it depends for its success on too many uncertain and difficult factors, not the least important of which is the manufacture of the prosthesis itself.

The second chapter,⁶⁰⁰ which is devoted to general principles, is most valuable but emphasizes points perhaps of questionable value, such as preparing the end of the bone for weight bearing. For this it is recommended that periosteum be removed for a distance of an inch (2.5 cm.) from the bone ends to prevent abnormal formation of the bone. This is at variance with Verrall's ideas.⁶⁰¹ He is a prominent English surgeon who has had much experience with amputations and who claims that special care of the periosteum is necessary. He states that injection of alcohol into the nerves causes alcoholic neuritis and should therefore be abandoned. He believes that terminal neuronia cannot be avoided. The end of the nerve should be placed where it is most protected, and crushing the nerve should be avoided. He goes on to state that adequate hemostasis should be employed rather than drainage.

In the Council's chapter on general principles it is stated that disarticulations, particularly of the knee, should give physiologically the best stumps. Cooperation of the limb makers is difficult to get.

Rogers⁶⁰² writes a strong paper on the superiority of the weight-bearing amputation through the knee joint, giving as advantages: The weight-bearing surface is large; all tissues in the vicinity are adapted

599. Amputation: Psychologic and Physiologic Principles in Amputations, report of the Council on Physical Therapy, J. A. M. A. **115**:1719-1720 (Nov. 16) 1940.

600. Amputation: General Principles Governing All Amputations, report of the Council on Physical Therapy, J. A. M. A. **115**:1799-1801 (Nov. 23) 1940.

601. Verrall, P. J.: Amputation Stumps and Artificial Limbs, Brit. M. J. **1**: 62-64 (Jan. 13) 1940.

602. Rogers, S. P.: Amputation Through Knee Joint, Physiologic Amputation, Mississippi Valley M. J. **62**:174-176 (Sept.) 1940.

to weight bearing; there is no tension on parts; control of the quadriceps femoris and hamstring muscles is maintained; long leverage for control of the hip is provided; good control of rotation is had because of the shape of the end; the bulbous end permits lifting of the prosthesis without a belt; there is minimum atrophy of the muscles of the thigh; good vascularity is assured; the distal femoral epiphysis is preserved in growing children.

In the Council's third chapter⁶⁰³ on amputations, sites are discussed. All amputations of the lower part of the leg through sites short of the toe and the anterior metatarsal bones is discouraged, except through the midtibia or higher if necessary, but not nearer than $2\frac{1}{2}$ inches (6.4 cm.) of the knee. Most amputations below the middle of the tibia necessitate amputations later because of circulatory difficulties. It is important to leave at least the head of the fibula, to permit easier rotation of the prosthesis. The value of amputation through the thigh in the prone position is explained; it facilitates exposure of the vessels and allows better tailoring of the flaps. Rees⁶⁰⁴ also advocates the prone position for amputations through the lower third of the femur, calling attention in addition to the points already noted, to the importance of suturing the tendons of the quadriceps muscles to those of the hamstring muscles, of using a single silk suture and also of keeping away from muscle tissue, especially when infection is possible.

In an effort to prevent all too frequent instances of embolism after amputation of a lower extremity Veal⁶⁰⁵ urges the high ligation of the femoral vein as a preliminary measure. An excellent diagram accompanies the article and indicates plainly how much venous surface with its entering veins is eliminated by this procedure without disturbing the circulation in the stump.

Hebb⁶⁰⁶ discusses amputation in light of his extensive experience in the World War. He states the ideal stump above the knee is 10 to 12 inches (25 to 30 cm.) long from the tip of the great trochanter with a posterior transverse scar $1\frac{1}{2}$ inches (3.8 cm.) above the end. The ideal stump below the knee is 6 inches (15 cm.) of tibia with the fibula 1 inch (2.5 cm.) shorter. Above the elbow the most satisfactory stump is 8 inches (20 cm.) from the tip of the acromion process; bone

603. Amputation: Sites of Election for Amputation, report of the Council on Physical Therapy, J. A. M. A. **115**:2174-2176 (Dec. 21) 1940.

604. Rees, C. E.: Amputation Through Lower Third of Femur: Modified Technique, California & West. Med. **53**:64-66 (Aug.) 1940.

605. Veal, J. R.: High Ligation of Femoral Vein in Amputations of Lower Extremities: Preliminary Report Based on Twenty-Eight Amputations of Thigh, J. A. M. A. **114**:1616-1619 (April 27) 1940.

606. Hebb, J. H.: Amputation Sites and After Treatment, J. Roy. Nav. M. Serv. **26**:144-147 (April) 1940.

should not be sectioned less than 3 inches (7.5 cm.) above the elbow. In the forearm a stump 7 to 8 inches (18 to 20 cm.) from the tip of the olecranon process is desirable. One as short as $3\frac{1}{2}$ inches (9 cm.) is of great value from the limb-fitting point of view. The importance of the elastic bandage dressing during convalescence is emphasized. [ED. NOTE: This is an excellent article giving the conclusion of a surgeon with a tremendous amount of experience.]

Contrary to the usual opinion of surgeons with wide experience with amputation, Guth,⁶⁰⁷ a surgeon at present with the German army, cites his own Pirogoff amputation as advantageous. The amputation was done twenty years ago. He has carried on an extensive country practice and once won second prize in a skiing competition. [ED. NOTE: It is felt, however, that the few successful results after a Pirogoff amputation are the exception rather than the rule.]

A note of warning is sounded by Leclerc⁶⁰⁸ urging patience in the surgical treatment of painful stumps, a large proportion of which he states improve spontaneously in the course of time. In cases in which the pain persists, particularly when the local injection of procaine hydrochloride gives temporary relief, lumbar sympathectomy or excision of the stellate ganglion in the upper extremity before nerve resection is performed is recommended.

Williams and O'Kane⁶⁰⁹ suggest a guide for operation and the level of amputation in lesions of the lower extremities associated with diabetes. The two major elements of the lesions are arterial insufficiency and infection. Often, if the question of blood supply is not carefully considered, the distressing appearance of septic forefoot in a patient with diabetes will unduly influence even an experienced surgeon to resort to amputation as the safest course. Instrumental observations the authors do not feel are necessary for a correct chemical evaluation of arterial insufficiency. [ED. NOTE: The article is well illustrated and deserves thorough reading. Their table of diagnostic criteria is well worth studying. The timely attention directed to this matter will result in the saving of many limbs which otherwise might have been unnecessarily amputated.]

Haddan,⁶¹⁰ who is president of the Association of Limb Manufacturers of America, Inc., declares Lisfranc, Chopart and Pirogoff

607. Guth, K.: Pirogoff Method of Foot Amputation, München. med. Wchnschr. 87:502-503 (May 10) 1940.

608. Leclerc, E. P.: Treatment of Painful Amputation Stumps, Presse méd. 48:667-669 (Aug. 21-24) 1940.

609. Williams, F. W., and O'Kane, T. J.: Clinical Classification of Lesions of Lower Extremities Associated with Diabetes: Guide for Operation and Level of Amputation, Arch. Surg. 40:685-693 (April) 1940.

610. Haddan, C. C.: Amputations to Obtain Greatest Functional Value, Rocky Mountain M. J. 37:440-446 (June) 1940.

stumps are unsatisfactory and that Syme stumps are inferior to amputations done below the knee. He recommends a 7 inch (17.8 cm.) tibia to be ideal for the lower part of the leg with the fibula 2 inches (5 cm.) shorter. A minimum stump he states is $1\frac{1}{2}$ inches (3.8 cm.) of the tibia, and in such cases the fibula should be removed. He condemns disarticulations through the knee joint and states that they are less efficient than Gritti stumps.

Close cooperation between the limb fitter and the surgeon is urged by Barling.⁶¹¹ He mentions the "sentimental appeal" of the Syme amputation, stating that it is particularly applicable to children. He emphasizes extreme conservatism in amputation of the upper extremities.

The technic of a shoulder girdle amputation is described in detail by Haggart,⁶¹² who states that the relatively simple method of identification and treatment of the subclavian vessels and brachial plexus is most effective. [ED. NOTE: The technic is a modification of that described by Littlewood⁶¹³ in 1922. Haggart's article is most important to remember when need arises for this rare but occasionally necessary operation.]

Artificial Legs and Arms.—Jordan⁶¹⁴ calls attention to a newly devised ischial strap seat which is claimed to be much more efficacious than the simple Thomas ring. It transfers the body weight from the tuberosity of the ischium to the lateral upright longitudinal bar of a double bar leg brace. It is also claimed that it is easier to construct than one with the direct ischial support. [ED. NOTE: This should be quite satisfactory if properly fitted.]

Dubois⁶¹⁵ states that an immediate or temporary prosthesis is of little value and urges the early use of a permanent apparatus. [ED. NOTE: Probably most surgeons favor the permanent apparatus except when emergencies such as arise from war conditions occur or when the economic factor must be considered. For children, for instance, one of us (J. W. W.) is of the opinion that a temporary prosthesis is of definite value. Most government rehabilitation authorities rule that a patient must have reached his full growth before he is allowed a permanent limb paid for by public funds.]

611. Barling, S.: Amputation of Extremities in Cases of War Wounds, *Post-Grad. M. J.* **16**:162-167 (May) 1940.

612. Haggart, G. E.: Technic of Interscapulothoracic Amputation, *Lahey Clin. Bull.* **2**:16-22 (July) 1940.

613. Littlewood, H.: Amputations at Shoulder and at the Hip, *Brit. M. J.* **1**: 381-383 (March 11) 1922.

614. Jordan, H. H.: New Ischial Seat Brace for Elimination of Weight Bearing, *J. Bone & Joint Surg.* **22**:1097-1100 (Oct.) 1940.

615. Dubois, M.: The Amputation of the Lower Extremities, *Helvet. med. acta* **6**:781-817 (March) 1940.

Braces.—Appreciating the actual danger of further damage to the spinal cord during the application of adequate support in the form of a plaster of paris cast to patients with injuries in the cervical portion of the spine and neurologic symptoms, Wegner and Munro⁶¹⁶ have attached for the purpose of immobilization a conventional back brace to the posterior lower part of a turnbuckle cervical extension brace. The importance of hyperextension, even during late convalescence, is emphasized. [ED. NOTE: This brace has been used in only 2 cases, and on looking at the illustrations one wonders if the addition of the spinal part is essential, except for injuries in the lower cervical or the upper dorsal region of the spine. If the usual hyperextension of the spine is obtained by the ordinary turnbuckle cervical brace with adequately placed generous anterior and posterior supports, one of us (J. W. W.) cannot see the necessity of extension of the spine save for fractures in the lowest cervical and the upper dorsal region of the spine. However, these are held satisfactorily by the Calot jacket.]

For fractured ribs and other injuries in the wall of the chest Steven⁶¹⁷ has devised a wide belt or binder in which there is an elastic element to allow expansion of the well side, the rest of it being nonelastic. It is claimed to give satisfactory immobilization on the side affected.

A rather complicated ambulance stretcher has been designed by Morrison.⁶¹⁸ It incorporates the idea of a hyperextension spinal frame for the safer transportation of persons with injuries of the back. There is an intrinsic spring traction arrangement for both the upper and the lower extremities. A central vertically placed padded board extending up to the perineum for temporary counter traction is a part of the equipment. [ED. NOTE: Since actual harm is done relatively frequently to patients with injuries of the spine by inexperienced ambulance drivers, the appearance of this apparatus, which should not be too expensive to manufacture, is welcomed, particularly as it is arranged so as to allow some degree of head traction. An added advantage is that roentgenograms of any part of the body, at least in one direction, can be taken without disturbing the patient.]

A restraint apparatus of simple and apparently efficient design has been described by Kaplan, Levinson and Lewin.⁶¹⁹ It consists of three 6 inch (15 cm.) unbleached muslin bands which are strapped around a

616. Wegner, W., and Munro, D.: Cervical-Spine Brace Which Reduces Use of Plaster Casts, *New England J. Med.* **223**:458-460 (Sept. 19) 1940.

617. Steven, R. A.: New Type of Belt for Splinting Chest, *California & West. Med.* **53**:84-85 (Aug.) 1940.

618. Morrison, G. M.: Stretcher Splint for Safely Transporting the Injured, *Am. J. Surg.* **48**:700-702 (June) 1940.

619. Kaplan, M.; Levinson, S. O., and Lewin, P.: Simple, Effective, Fabric Restraint-Splint, *J. A. M. A.* **115**:1098-1099 (Sept. 28) 1940.

mattress at suitable levels, so that other 2 inch (5 cm.) bands can be stitched to them; these buckle around both extremities just above the ankle, the knee and the wrist. Another wide muslin band passes around the foot of the bed; to this are fastened two other 2 inch (5 cm.) bands which hold the forefoot securely in place preventing drop foot and rotation at the same time. If necessary, it is thought that other bands might be used around the chest, the head and the pelvis for further immobilization of an intractable patient, holding him down in Gulliver fashion without risk of injury.

Dubs⁶²⁰ tells of a quickly adjustable temporary splint for transportation; it is for both the upper and the lower extremities, different countertraction crutches being used for the arms and for the legs. The apparatus is original in that a single four-edged bar is used to which the various attachments for traction and countertraction are applied. Its chief advantages are its ease of application and the fact that it can be applied over clothing.

A modification of the Böhler abduction shoulder brace is presented by Parsons and Hart.⁶²¹ It does not extend down over the iliac crest on the affected side. It is claimed that this extension down over the crest is not necessary and that if it extends down just a little below the costal border it is just as efficient and allows the patient much more freedom. [ED. NOTE: This departs considerably from the usual custom in all abduction braces and should be thoroughly tried out before being accepted.] They also recommend that plaster shoulder spicas should never be applied with the patient under anesthesia. [ED. NOTE: One of us (J. W. W.) does this as a routine.]

Hundemer⁶²² describes a Cramer or Böhler support which with stability allows the turning of the upper arm as well as movements in vertical and horizontal directions. [ED. NOTE: If the device permits all this flexibility, it is difficult to understand how it can be stable.]

Traction Apparatus.—Baker and Hawkes⁶²³ describe an apparently easily assembled trapezoidal apparatus hinged at its four corners and controlled with an internal diagonal turnbuckle which serves as the basis of the traction arrangement in which the well leg is used to fix and reduce the injured leg, the pelvis serving as a fulcrum. The apparatus is clamped onto the casts regularly applied in this method of treatment,

620. Dubs, J.: New Extension and Fixation Splint for Arm for Transportation Purposes, *Schweiz. med. Wchnschr.* **70**:193-195 (March 2) 1940.

621. Parsons, K. O., and Hart, A. T.: Splinting Fractures of Humerus, *Brit. M. J.* **1**:726-728 (May 4) 1940.

622. Hundemer, W.: Adjustable Arm Splint Permitting Turning of Upper Arm, *München. med. Wchnschr.* **87**:568-569 (May 24) 1940.

623. Baker, M., and Hawkes, S. Z.: New Apparatus for Well Leg Traction, *Am. J. Surg.* **49**:523-525 (Sept.) 1940.

and the push-pull action is instituted with the turnbuckle as desired. The authors briefly discuss the type of injuries for which the apparatus is adapted, stating justifiably that it is best suited for the intertrochanteric fracture. [ED. NOTE: In the illustration accompanying the article the leg casts seem unusually short. To be truly effective and immobilize the knees satisfactorily, they should go up further toward the groin than pictured. Unfortunately nothing is mentioned about transfixing plaster-incorporated pins. It is to be feared that if this device is employed by an inexperienced surgeon and any real degree of traction is applied, distressing sloughs will result.]

Overton⁶²⁴ advocates the use of a simple foot plate combined with a spreader for use in traction of the skin on the lower extremity. In order to prevent drop foot, traction is applied to a cross bar on the gutter foot piece posterior to or below the spreader about an inch (2.5 cm.). [ED. NOTE: This simple apparatus might be of more value if to prevent rotation of the leg one of the cross bars could be extended a few inches on either side and bent down to rest on the surface of the bed.]

The value of intrinsic elastic band traction replacing weight and pulley equipment is advocated by McKinnon.⁶²⁵ He sets forth its advantages in a most convincing manner. In order to know just how much traction is being applied he suggests that a small 25 pound (11.3 Kg.) spring balance be hooked up in series with the rubber bands. [ED. NOTE: This method has been used for years by one of us (J. W. W.) with complete satisfaction. A spring balance manufactured by Chatillon is most satisfactory.]

Rogge⁶²⁶ describes a sliding splint for immobilization and extension at the front of fractured legs. The splint is said to have been valuable during the World War. [ED. NOTE: From the description, the arrangement appears to be too simple to be efficient, and it is to be feared that except for emergencies such as occur in military engagements it would be impracticable.]

Skeletal cranial traction for fractures and dislocations in the cervical region of the spine is recommended by Zorn,⁶²⁷ who uses a wire loop beneath the outer table of the skull. [ED. NOTE: The apparatus he

624. Overton, L. M.: Simple Foot Plate for Use in Skin Traction on Lower Extremities, *J. Iowa M. Soc.* **30**:110 (March) 1940.

625. McKinnon, S. D.: Fractures—Elastic Band Traction, *Canad. M. A. J.* **43**:324-327 (Oct.) 1940.

626. Rogge, H.: Sliding-Splint Bandage for Splinting and Nonsurgical Extension of Leg Fractures at Front, *München. med. Wchnschr.* **87**:281-284 (March 15) 1940.

627. Zorn, L.: Cranial Wire Extension in Fractures of Cervical Vertebrae, *Zentralbl. f. Chir.* **67**:850-852 (May 11) 1940.

describes does not appear to be nearly so efficient nor so easy to apply as those used in this country.]

Another orthopedic table is described by Saigo.⁶²⁸ In it the arrangement for vertebral traction, especially in the cervical region, has been emphasized. [ED. NOTE: Skeletal traction is not mentioned, and it is doubtful whether any new principles have been employed.]

Plaster Cast Technic.—The advantages of plaster of paris bandages prepared in a hospital are taken up by McLin⁶²⁹ in a well written article. The capacity of satisfying the desires of individual surgeons as well as saving money is stressed. He urges the employment of periodic setting time tests and calls attention to the importance of having a dry storage place.

Girdlestone⁶³⁰ describes the cream-fabric method advocated by Trueta for rapid application of the plaster cast. Excellent pen and ink illustrations accompany the article. He also gives rather implicit directions to the beginner in the plaster technic.

Recognizing the difficulty of removing plaster casts, particularly skin plaster, Bickford⁶³¹ has devised an ingenious can opener method. The cast is cut by winding up on a heavy hemostat a section of piano wire, placed under the cast when it was applied. For casts more than $\frac{1}{2}$ inch (1.3 cm.) thick, he doubles the wire back on itself as many times as needed. No. 22 (English gage) wire is the heaviest piano wire that can be satisfactorily wound up on a hemostat, and any size smaller than no. 26 is too weak. [ED. NOTE: It sounds simpler and more practical than some other methods which use a somewhat similar principle. It is worth trying.]

Cogswell and Thomas,⁶³² in discussing windowed casts, advise that the window be cut when the plaster is fresh and the edges beveled so that the part nearest the skin is larger than the external opening. This will prevent the distressing bulging of edematous tissue through the aperture, and the necessary amount of skin pressure over the wound can be more easily maintained. [ED. NOTE: Waterproofing the plaster plug will probably cause too much sweating to be satisfactory unless the dressings are frequent or unless the window is small.]

628. Saigo, V.: Mechanism of Vertebral Fractures, Orthopedic Table for Reduction and Fixation, *Zentralbl. f. Chir.* **67**:106-110 (Jan. 20) 1940.

629. McLin, W. C.: Hospital-Made Plaster Bandages, *Mod. Hosp.* **55**:51-53 (Aug.) 1940.

630. Girdlestone, G. R.: Plaster-of-Paris, *Lancet* **2**:287-291 (Sept. 7) 1940.

631. Bickford, R. G.: Rapid and Painless Method of Removing Plaster Casts, *Brit. M. J.* **1**:539-540 (March 30) 1940.

632. Cogswell, H. D., and Thomas, C. A.: Method for Protecting Skin in "Windowed" Unpadded Casts, *Am. J. Surg.* **49**:409-410 (Sept.) 1940.

The Trueta treatment of war wounds with plaster casts is reported favorably by Ricard, Francillon, Deplante and Mathevon.⁶³³ They emphasize the importance of having experienced men to apply the cast, as success depends largely on the manner of application. They urge delay in extracting projected fragments of bone and warn about the high incidence of ankylosis in patients with injured joints.

To hold bivalve casts neatly and accurately together, Rounds⁶³⁴ recommends a folded-over strip of hard coated rapid-drying plaster to which nickle-plated boot hooks have been riveted at the edges of the plaster halves. [ED. NOTE: As they seem to be fastened to the cast only by the cementing property of the plaster strips, one wonders how well they will stay in place if any real tension is placed on them. The need for such an arrangement is admitted to replace unsightly adhesive straps, and it is hoped that this suggestion will prove practicable.]

To replace clumsy and noisy walking irons, injurious to furniture and flooring, Stryker⁶³⁵ recommends that rubber heels be incorporated in the sole of the plaster casts where weight bearing is desired.

As a substitute for a steel and leather back brace, Mitchner⁶³⁶ describes a suspender-like arrangement made of plaster reenforcements which he claims is efficient. For particularly heavy people he reenforces the strips which are well padded underneath with molded duralumin or tin. [ED. NOTE: The idea hardly seems practicable but may be worth a trial by the plaster enthusiast.]

Roentgen Technic.—In a reassuring article Garland and Morrissey⁶³⁷ state that although iodized poppyseed oil (30 to 60 per cent) enters the cranium in two thirds of the cases in which it is used as a diagnostic aid in the spinal canal, it causes no trouble. What symptoms exist may be definitely attributed to causes other than the presence of the oil. [ED. NOTE: This is not the general belief about iodized poppyseed oil. Physicians are still awaiting the discovery of an absorbable opaque substance for this work, regardless of optimistic opinions about the presence of the oil to the contrary.]

633. Ricard, Francillon, Deplante and Mathevon: *Therapy of Extensive Traumatism of Extremities by Plaster Cast and Rare Dressings: Study Based on Experience in Spanish War*, Lyon chir. **36**:573-583, 1940.

634. Rounds, R. C.: *Method of Maintaining Cut Edges of Split and Bivalved Casts in Accurate Apposition*, J. Bone & Joint Surg. **22**:1088-1089 (Oct.) 1940.

635. Stryker, H. H.: *Rubber Heels for Walking Casts*, Surg., Gynec. & Obst. **70**:841-842 (April) 1940.

636. Mitchner, J. M.: *Double-Bar Plaster Black Support*, J. Bone & Joint Surg. **22**:456-457 (April) 1940.

637. Garland, L. H., and Morrissey, E. J.: *Intracranial Collections of Iodized Oil Following Lumbar Myelography*, Surg., Gynec. & Obst. **70**:196-210 (Feb.) 1940.

A rather complicated arrangement for making accurate roentgenograms of the neck of the femur is reported by McKenna.⁶³⁸ A shock-proof x-ray unit is placed beside a radiolucent perineal post measuring 4 inches (10 cm.). A plate holder is placed over the lateral aspect of the hip. The technic is further complicated by the suggestion that two portable x-ray units be used. [ED. NOTE: It is the opinion of one of us (J. W. W.) that a lateral view obtained by flexing and rotating the hip is far easier to procure, particularly if the patient can be placed on a genitourinary x-ray table with a Bucky diaphragm and a stationary tube. A technic of this type has been used by one of us (J. W. W.) for years with complete satisfaction, and he feels that taking lateral views in the horizontal plane of the table is not necessary.]

An important discussion of errors in the interpretation of roentgenograms has been published by Goldhamer and Swanberg.⁶³⁹ [ED. NOTE: One point was not mentioned which most orthopedic surgeons consider important, namely, that every roentgenogram should be seen and interpreted by the surgeon ordering it as well as by the roentgenologist. In taking certain roentgenograms it is most important to have the surgeon either present or know exactly how it is taken.] The authors correctly emphasize the importance of knowing just where the central ray passes through the part shown in the roentgenogram. [ED. NOTE: One of us (J. W. W.) believes it would be most desirable to have some way of recording the location of this central ray on the film.]

White⁶⁴⁰ has evolved a relatively simple method of graphically recording the discrepancy of legs of different length. The discrepancy is measured by the vertical difference between the horizontal lines drawn tangent to the top of the heads of the femurs on a roentgenogram of the pelvis taken while the patient is pushing both feet against a horizontal foot board on the usual Bucky x-ray table. He admits that there is a small distortion with this method, but since the same factor persists throughout other measurements in the same case, it tends to cancel itself out as an error. He has found this method most satisfactory and far more accurate than the bony landmark-tape line measurement.

Miscellaneous.—Albee⁶⁴¹ describes a new type of fracture table designed to facilitate extensive roentgen examinations and yet sacrifice

638. McKenna, H.: Device for Making Accurate Roentgenograms of Neck of Femur During Reduction, *Surg., Gynec. & Obst.* **71**:808-810 (Dec.) 1940.

639. Goldhamer, K., and Swanberg, H.: Errors in Roentgen Interpretation. *Mississippi Valley M. J.* **62**:136-142 (July) 1940.

640. White, J. W.: Practical Graphic Method of Recording Leg Length Discrepancies, *South. M. J.* **33**:946-949 (Sept.) 1940.

641. Albee, F. H.: Albee-Comper Fracture Table, *Am. J. Surg.* **47**:160-166 (Jan.) 1940.

none of the advantages of the most up-to-date operating table. Many new improvements are claimed for it, especially in regard to the care of injuries to the spine.

Santy and de Willencourt ⁶⁴² have devised an apparatus which they state can be attached to any operating table for the purpose of holding the patient in a position of ventral decubitus during the application of a plaster cast employed in the treatment of conditions involving the spinal column. [Ed. NOTE: While the apparatus appears ingenious, it does not appear to be practical for all types of cases.]

XX. RESEARCH

Vitamins.—Wille ⁶⁴³ uses a preparation containing water-soluble vitamin C and B₁ in their natural forms in the treatment of arthritis, particularly arthritis deformans in elderly women. The aim of his report is to prompt physicians to make further use of water-soluble vitamins in treating arthritic conditions. He prefers that the vitamins be given in their natural form, despite the fact that the exact nature of their action has not been established.

Liu ⁶⁴⁴ states that the fundamental defect involved in osteomalacia is an altered state of the intestinal tract on account of which calcium is either not absorbed or absorbed with difficulty. Administration of vitamin D will aid the absorption of calcium from the intestinal tract, but in addition a diet high in calcium should be given. Vitamin D when taken in large doses will be stored in the body if not used, and this supply will then be drawn on as needed to maintain a normal calcium balance.

Spies ⁶⁴⁵ states that vitamin B₆ (pyridoxine) at times has a dramatic beneficial effect in relieving muscular weakness and rigidity. It also lessens the rigidity in some cases of paralysis agitans. The symptoms of deficiency of vitamin B₆ may be adequately treated by intravenous injection of 50 mg. of this vitamin in physiologic solution of sodium chloride. Considerable improvement has been seen after its use in cases of pseudo hypertrophic muscular dystrophy.

642. Santy and de Willencourt: Apparatus for Application of Plaster Cast in Ventral Decubitus in Spinal Disturbances, *Lyon chir.* **36**:614-617, 1940.

643. Wille, E.: Vitamins C and B₁ in Articular Rheumatism, *Fortschr. d. Therap.* **16**:118-122 (April) 1940.

644. Liu, S. H.: Role of Vitamin D in Calcium Metabolism in Osteomalacia, *Chinese M. J.* **57**:101-118 (Feb.) 1940.

645. Spies, T. D.; Hightower, D. P., and Hubbard, L. H.: Some Recent Advances in Vitamin Therapy, *J. A. M. A.* **115**:292-297 (July 27) 1940.

Stone ⁶⁴⁶ writes that vitamin E (given in the form of wheat germ oil) produces definite improvement in cases of muscular dystrophy; the addition of the vitamin B complex increases its efficacy.

Steinberg ⁶⁴⁷ reports that for muscular dystrophy one may give 2 cc. each day of wheat germ oil mixed with the vitamin B complex and that this promptly results in increased resistance to fatigue, in improvement of appetite and in normal muscles replacing rubbery muscles. For long-standing muscular dystrophy with contracture deformities, the administration of 4 to 6 cc. per day of wheat germ oil is suggested; no unpleasant after-effects have been noted. This dosage is also of value in the treatment of primary (but not of secondary) fibrositis.

In 1937 Mouriquand, Dauvergne, Tête and Edel ⁶⁴⁸ showed that by administration over a long period of a diet low in vitamin C it is possible to produce a syndrome of chronic ankylosing rheumatism with osseous decalcification in the epiphysis and metaphysis and osseous production at the periphery. They found that neither a scorbutigenic diet alone nor a scorbutigenic diet to which a small amount of vitamin C had been added would produce this syndrome. However, they now find that if small amounts of vitamin C and lemon juice are added to the scorbutigenic diet these changes are produced. They have not yet determined precisely which factors in lemon juice produce the osteophytic change but are continuing their experiments. They conclude that this osteophytic change like ordinary periosteoses is resistant to large doses of vitamin C, is irreversible and belongs to the group of paravitaminoses.

Steinberg ⁶⁴⁹ reports 30 cases of primary fibrositis treated by wheat germ oil in doses of 2 to 8 cc. daily for two to four months. Eight patients showed definite improvement in muscular soreness and stiffness; 12 had no relief.

Endocrine Secretions and Their Relation to Growth and Development of Bone.—Johnston ⁶⁵⁰ states that sexual maturation in the normal

646. Stone, S.: Treatment of Muscular Dystrophies and Allied Conditions: Preliminary Report on Use of Vitamin E (Wheat Germ Oil), *J. A. M. A.* **114**: 2187-2191 (June 1) 1940.

647. Steinberg, C. L.: Vitamin E in Treatment of Fibrositis, *Am. J. M. Sc.* **201**:347-459 (March) 1941.

648. Mouriquand, G.; Dauvergne, M.; Tête, H., and Edel, V.: Osteophytes Due to Chronic Avitaminosis, *Compt. rend. Acad. d. sc.* **210**:515-516 (April) 1940.

649. Steinberg, C. L.: Vitamin E in Treatment of Fibrositis, *Am. J. M. Sc.* **201**:347-349 (March) 1941.

650. Johnston, J. A.: Factors Influencing Retention of Nitrogen and Calcium in Period of Growth: Puberty in the Normal Girl and in the Girl with the Minimal Reinfection Type of Tuberculosis, *Am. J. Dis. Child.* **59**:287-309 (Feb.) 1940.

girl is accompanied by depression in the retention of calcium and nitrogen. This may precede or follow the menarche by several months, since the menarche is just one incident in this phase of growth. A physiologic rise and fall in the basal metabolic rate also occurs during puberty, and there is a direct parallelism between the retention of calcium and nitrogen and the basal metabolic rate. Evidence is presented which suggests that this phenomenon of decreased retention of calcium and nitrogen may be a contributing factor in the increased incidence of the reinfection type of tuberculosis in girls of this age group.

Avery, Scott and Conrad ⁶⁵¹ found appreciable rise in blood calcium when chickens were given injections of estrone (theelin). When the administration of estrone was discontinued, the blood calcium came down to that of the control animals.

Ely and Phillips ⁶⁵² injected estradiol benzoate into immature female rats in sufficient quantity to produce marked effects on uteri and ovaries but observed no demonstrable effects on the skeletal development. This does not confirm the results of the experiments of Gardner and Pfeiffer, ⁶⁵³ who report that estradiol benzoate causes the marrow cavities of female mice to be replaced almost completely by bone.

Sutro ⁶⁵⁴ concludes that injection of estradiol benzoate into immature female and male mice in various doses stimulates the proliferation of new bone in the medullary cavities of certain bones and especially in those of the lower end of the femur and the upper end of the tibia. The proliferation begins around the zone of provisional ossification and advances into the diaphysial portion of the bone. There is no increase in periosteal activity.

Wentworth, Smith and Gardner ⁶⁵⁵ injected estradiol benzoate into mice and report that it produces significantly higher concentrations of inorganic substances in the femurs and in the pelvis of mice receiving this substance than in control mice or in mice receiving testosterone propionate or estradiol benzoate plus testosterone propionate.

Rubinstein and Solomon ⁶⁵⁶ injected testosterone propionate intraperitoneally into male albino rats, beginning at the age of 26 days with

651. Avery, T. B.; Scott, H. M., and Conrad, R. M.: Blood Calcium Levels of Fowl Following Injections of Theelin, *Endocrinology* **27**:83-86 (July) 1940.

652. Ely, J. O., and Phillips, R. L.: Effect of Alpha Estradiol Benzoate on Skeletal Development of Immature Rats, *Endocrinology* **27**:661-663 (Oct.) 1940.

653. Gardner, W. U., and Pfeiffer, C.: Skeletal Changes in Mice Receiving Estrogens, *Proc. Soc. Exper. Biol. & Med.* **37**:678-679 (Jan.) 1938.

654. Sutro, C. J.: Effects of Subcutaneous Injection of Estrogen upon Skeleton in Immature Mice, *Proc. Soc. Exper. Biol. & Med.* **44**:151-154 (May) 1940.

655. Wentworth, J. H.; Smith, P. K., and Gardner, W. U.: Composition of Bones of Mice Receiving Estrogens and Androgens, *Endocrinology* **26**:61-67 (Jan.) 1940.

656. Rubinstein, H. S., and Solomon, M. L.: Growth-Stimulating Effect of Testosterone Propionate, *Proc. Soc. Exper. Biol. & Med.* **44**:442-443 (June) 1940.

doses of 0.05 mg. daily and continuing for fifty-three days. They found a significant growth-stimulating effect. Larger doses of the same preparation caused a growth-inhibiting effect.

McCullagh and McGurl⁶⁵⁷ conclude in regard to epiphyseal closure that an increase in the rate of epiphyseal maturity beyond normal should serve as a warning to those who are inclined to give large doses of testosterone propionate to immature persons. They emphasize strongly that dwarfing might be caused by such doses being given to patients who have not attained normal adult stature.

The Source of Creatine.—Borsook and Dubnoff⁶⁵⁸ claim a specific sensitive analytic method for the study of the precursors of creatine in animals. They use a soil bacterium which specifically destroys creatine and creatinine. They have found that slices of the liver of the cat, the rabbit and the rat are able to convert glycocyamine to creatine. In their experiments they have observed an increase of from five to twenty times the amount of creatine originally present in the slices of liver. This conversion requires methylation by the liver tissue. If methionine is added, the amount of creatine formed is 50 per cent greater on the average than if methionine is not added. Methionine is the only substance yet found by the authors among a large number of amino acids, methylated amines and other compounds which is able to effect this increase in methylation in the liver of the rat. Other animals and other substances are now being studied.

Borsook and Dubnoff⁶⁵⁹ follow up their previous paper with an experimental study. In this, experiments showed "that glycocyamine can be methylated by the liver of every animal examined. The stimulating effect of methionine observed with rat liver was found with some but not with all the other animals. The kidney appears to be unimportant (except in the pigeon) for the methylation of glycocyamine with or without methionine." These findings are interpreted as indicating that creatine normally is formed by the methylation of glycocyamine in the liver.

Retention and Utilization of Calcium.—Pierce, Daggs, Meservi and Simcox⁶⁶⁰ present the results of their investigation to determine the

657. McCullagh, E. P., and McGurl, F. J.: Effects of Testosterone Propionate on Epiphyseal Closure, Sodium and Chloride Balance and on Sperm Counts, *Endocrinology* **26**:377-384 (March) 1940.

658. Borsook, H., and Dubnoff, J. W.: Formation of Creatine from Glycocyamine in Liver, *J. Biol. Chem.* **132**:559-574 (Feb.) 1940.

659. Borsook, H., and Dubnoff, J. W.: Creatine Formation in Liver and in Kidney, *J. Biol. Chem.* **134**:635-639 (July) 1940.

660. Pierce, H. B.; Daggs, R. G.; Meservi, A. B., and Simcox, W. J.: Retention of Calcium and Phosphorus by Pre-School Children, *J. Nutrition* **19**:401-414 (April) 1940.

relative availability of calcium and phosphorus in milk and in so-called fortified food. The fortified food consisted of cereal to which a mixture of calcium, sodium and iron phosphates had been added. The subjects were 4 girls and 6 boys from 3 to 6 years of age. The calcium level of each subject was brought to saturation. The subjects were then divided into two groups of 2 girls and 3 boys each. The periods of diet were reversed in each group to rule out weather or seasonal effects. They were maintained on carefully regulated basal diets.

The authors conclude that there is no appreciable difference of retention of calcium and phosphorus with the use of the different salts; utilization of calcium and phosphorus was equally good with milk and with fortified cereal. The daily storage of calcium was 11 to 12 mg. per kilogram of body weight; the daily storage of phosphorus was 7 to 8 mg. per kilogram of body weight. About 19 per cent of the calcium and 11 per cent of the phosphorus were retained. To obtain maximal retention of calcium it was necessary to give over 700 mg. daily.

Kempster and associates⁶⁶¹ state that previous experiments have shown that only about one fifth of the calcium ingested in milk is utilized. Experiments were made to determine the utilization of the calcium of dicalcium phosphate. Six small boys served as subjects. They were fed two levels of calcium. It was found that the utilization of calcium of dicalcium phosphate by these subjects averaged 19.5 per cent. Hence the authors conclude that there is no superiority of dicalcium phosphate over milk as a source of calcium.

Arthrography.—Tarafa⁶⁶² concludes that the injection of a contrast medium into the joints is indicated in cases in which one wishes to examine the soft parts within the joint, such as a meniscus, the capsule or a cruciate ligament, or some foreign body, tumor or other intra-articular change. Penetration of air between the plate and the meniscus of the tibia is seen in the arthropneumoroentgenogram when detachment of the meniscus is present. Tear of the meniscus appears as a more or less irregular interruption at the site of the rupture. Tearing off of the cruciate ligaments produces some change in the normal picture, often associated with fracture of the spine of the tibia. With arthritis an enlargement of the capsule and irregularities in its walls are observed. An intra-articular tumor shows a perfectly defined outline while an extra-articular tumor squeezes and displaces the capsule. Loose bodies in the joint appear well defined. With Charcot's knee joint.

661. Kempster, E., and others: Utilization of Calcium of Dicalcium Phosphate by Children, *J. Nutrition* 20:279-287 (Sept.) 1940.

662. Tarafa, J. I.: Arthropneumoradiography, *Cir. ortop. y traumatol.*, Habana 8:3-17 (Jan.-March) 1940.

besides a marked increase of the joint space and abnormal features of the joint surface, an almost complete destruction of the soft parts is evident.

Paas⁶⁶³ describes a method of visualizing the knee joint by the injection of a contrast material known as "abrodil" (skiodan N. N. R.) in a 20 per cent solution and of one known as "perabrodil" (diodrast N. N. R.) in a 35 per cent solution. Experimental work was done on dogs. The author finds that the resorption time of the material depends on both the age of the subject and the condition of the joint. With acute inflammation of the capsule of the joint the resorption is faster than normal. Active and passive motion also increase the rapidity of resorption. The tension and space of the joint depend on the position of the joint during examination. In extension the anterior part of the capsule has the least tension; in flexion the posterior part has the least tension. The normal capsular apparatus has marked elasticity. In advanced age after a long period of freedom from weight bearing, there is a shortening of the structure of the capsule with loss of elasticity. Freedom from weight bearing and advanced age diminish the ability of the capsule to resorb the contrast materials.

The Dynamics of Muscle and Bone.—Heppel⁶⁶⁴ presents the results of his study of the changes that take place in muscles when stimulated, especially changes in potassium, sodium chloride and water, as related to the age of the animal. All of the work was done on young rats at the age of 5 to 6 weeks. The changes observed in these animals are twice as great as in older rats. Heppel also studied the influence of diet, tension, duration of stimulation and poisoning with monoiodoacetic acid on the electrolyte changes.

His conclusions are as follows:

1. The loss of potassium on stimulation of rat muscles is progressively greater as the duration of contraction is increased. After 30 minutes there is no further change, at least for another half-hour.
2. The changes in chloride and water are almost maximal after 5 minutes of stimulation; after 1 hour the changes are very much reduced in magnitude.
3. The individual variations in the water changes follow closely those of chloride, but there is no correlation with the variations in the potassium changes. The potassium loss and the chloride gain apparently bear a different relationship to the contraction processes.
4. Previous work relating to the changes during recovery is confirmed.
5. Young rats of about 6 weeks of age are able to lose more potassium from their muscles on stimulation than is the case for adult rats.

663. Paas, H. R.: Study of Capsule by Means of Positive Contrast Fluid and Fluoroscopy, *Deutsche Ztschr. f. Chir.* 252:478-498, 1939.

664. Heppel, L. A.: Effect of Age and Diet on Electrolyte Changes in Rat Muscle During Stimulation. *Am. J. Physiol.* 128:440-448 (Feb.) 1940.

6. Feeding diets low in potassium and poisoning with monoiodoacetic acid have little or no effect on the potassium changes during stimulation. Previous work on the influence of tension is confirmed.

Elftman⁶⁶⁵ has previously described a method for determining the muscle forces and their activity as applied to walking. Now he describes the same method as applied to running.⁶⁶⁶ The determinations were made by analysis of photographic films. The moments of force resulting from the muscles acting about the joints of the limbs and the rates at which they do work were determined for a running step. The energy requirement arrived at in this way represents a minimum for the step concerned; it does not include energy used for the maintenance of tension in muscles which are not changing in length or for the duplication involved in the simultaneous action of antagonists.

The muscles of the limb did work at the rate of 2.61 horsepower. If all the muscles of the body were included and no energy was lost through friction, the rate would be at least 2.89 horsepower.

Work done by the muscles of the limb was divided as follows: against wind resistance, 0.15 horsepower; fluctuations in the total energy of the body, 1.37 horsepower; distribution of energy between the parts of the body, 1.09 horsepower. If one joint muscles were present, additional work at the rate of 1.36 horsepower would be necessary. The saving of this amount by two joint muscles illustrates the importance of the disposition of muscles in determining muscular work.

Miller and Darrow⁶⁶⁷ present some experimental work which attempts to throw some light on whether changes in the electrolyte pattern within the muscle cell affect the ability of the cell to perform work. Other investigators have shown that muscle activity may be affected by rapid changes in extracellular electrolyte. The experimental procedure used by the authors altered the potassium of skeletal muscle, and they studied the response of the muscle to repeated tetanic stimulation. They conclude that there is no direct relation between the amount of potassium in the muscle or serum and the type of response to the tetanic stimulation obtained. It is felt that this lack of correlation in the data is evidence against the belief that the myasthenia noted in adrenal insufficiency is due specifically to increase in the potassium of skeletal muscle.

665. Elftman, H.: Forces and Energy Changes in the Leg During Walking. *Am. J. Physiol.* **125**:339-356 (Feb.) 1939; Function of Muscles in Locomotion. *ibid.* **125**:357-366 (Feb.) 1939.

666. Elftman, H.: Work Done by Muscles in Running. *Am. J. Physiol.* **129**: 672-684 (June) 1940.

667. Miller, H. D., and Darrow, D. C.: Effect of Changes in Muscle Electrolyte on Response of Skeletal Muscle to Tetanic Stimulation with Particular Reference to Potassium. *Am. J. Physiol.* **129**:264-270 (May) 1940.

Milch⁶⁶⁸ presents the results of his studies of the relation of the contour of bone to forces exerted on bone. His studies were made by subjecting bone models made with polymerized phenylformaldehyde resins to stress. When such resins are subjected to stress they realine themselves to fit the molecular structure to which they have been applied, depending on the changes of the lines of stress. Such lines of stress can be visualized under polarized light and then photographed. The author studied models of normal bone and bone which had been alined by osteotomies. He also studied an os calcis and a whole foot.

When the outline of the normal femur was compressed, several interesting phenomena were observed. The arrangement of the lines of stress was found to be reminiscent of the trabecular structure seen on longitudinal section of the femur. When the model was shifted first to one side and then the other to simulate abduction and adduction under weight bearing, these stress lines shifted so that they resembled first one and then the other of the longitudinal trabecular systems. The stress lines seemed to run between the two points of compression and apparently did not radiate into the trochanteric region to any noticeable extent. The greater number of stress lines appeared to be on the medial side of the shaft, toward the line of the mechanical axis of the normal femur. The stress lines seemed to stop in an area which was situated close to the normal epiphysial zone. This stress pattern was repeatedly reproduced. It could be modified by adding the element of traction to that of compression.

The author suggests that this method of analysis could be applied to a great variety of clinical and theoretic problems for study, and eventually a fuller knowledge of the predetermined lines of stress when planning realignments of the extremities would be gained.

668. Milch, H.: Photo-Elastic Studies of Bone Forms, *J. Bone & Joint Surg.* **22**:621-626 (July) 1940.

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CLINICAL USE OF HEPARIN IN THE PERITONEUM FOR THE PREVENTION OF ADHESIONS

REPORT OF FOURTEEN CASES

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In 1940 we presented two papers¹ on the use of heparin in the prevention of peritoneal adhesions in the dog. In these reports it was shown that the reformation rate of adhesions after the intraperitoneal administration of effective doses of heparin was in the neighborhood of 30 per cent, while the average reformation rate among controls was 147 per cent. Since the publication of these papers, laboratory experimentation has been continued, and an extensive series of experiments will be reported elsewhere. It can be stated here that these experiments confirm the conclusions in the reports of our earlier work. It is our opinion that this method of diminishing the number of reformed adhesions after division is theoretically sound, and it has been proved to be practically effective in the dog.

The mechanism of this effectiveness is believed to consist in the diminution of the coagulability of the serous exudate which is the first response of the peritoneum to injury. "The process of organization always takes place in fibrin, and cannot take place without fibrin. It seems logical, therefore, to expect that the prevention of the formation of fibrin will prevent the organization that is the essential element of a permanent pathologic nature."^{1a}

To the action of heparin in preventing the coagulation of the exudate is added of course its action in preventing the deposition of fibrin in the cut ends of blood vessels. Without adequate hemostasis it is obvious

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1. Lehman, E. P., and Boys, F.: (a) The Prevention of Peritoneal Adhesions with Heparin: An Experimental Study, *Ann. Surg.* **111**:427-435, 1940; (b) Heparin in the Prevention of Peritoneal Adhesions: Report of Progress, *ibid.* **112**:969-973, 1940.

that the use of heparin in the peritoneum will be associated with intra-abdominal hemorrhage. Until this fact was realized there were a number of deaths from this complication among the experimental animals. After more scrupulous efforts were made to control all oozing points before the introduction of heparin, this danger apparently ceased to exist. There have been as many as seventy-five consecutive applications of heparin to the peritoneum after the division of adhesions in the dog with no bleeding whatever.

The experimental studies just summarized were of course directed toward ultimately trying the method on human beings, provided it could be made safe. During recent months 14 patients have been treated with heparin given intraperitoneally after the division of adhesions. Seven of these patients were treated under our supervision; the others were treated at the different clinics indicated in the protocols.

Various surgeons cooperated by using this method and by furnishing abstracts of their cases.

This report is the first on the clinical use of heparin for the prevention of the reformation of intraperitoneal adhesions.

In an earlier paper ^{1a} we pointed out that an enormous number of patients must be treated with heparin before a sufficient number will have come to relaparotomy or autopsy to provide a basis for judging the efficiency of the method. Since we still hold this opinion, it is obvious that in the present paper we can make no claims for the effectiveness of the method in the human being. We present the data contained herein to throw light on the safety and the dangers of the method and to put before the medical profession a probably adequate technic for the intraperitoneal administration of heparin in properly selected cases.

INDICATIONS AND CONTRAINDICATIONS

Until greater experience has been had in clinical application, the use of heparin should be limited to cases of acute partial or complete intestinal obstruction due to adhesions and particularly to cases in which previous operations have been performed for obstruction or repeated threatening attacks. In other words, heparin should be used only in that group of desperate cases in which one is willing to accept the hazard of an insufficiently tried method in preference to a future risk of significant proportions.

The one important and essential contraindication to the use of heparin in the abdomen is the presence of an oozing peritoneum after adhesions have been divided. A recent experience hereinafter reported leads us to the further conclusion that heparin should not be used when granulation or subacute inflammatory tissue is present whether hemostasis seems complete or not.

TECHNIC

Before operation, the pulse rate, the erythrocyte count, the percentage of hemoglobin, the systolic and the diastolic blood pressure and the blood coagulation time must be recorded. These determinations must be made every two hours for at least six hours after each administration of heparin and immediately before the next administration. The first four of these are of importance in detecting possible intraperitoneal hemorrhage after the use of heparin. As the drug is absorbed into the blood stream from the peritoneum to some degree, determination of the coagulation time is indicated. The apex of the curve of increased blood coagulation time is reached about two hours after the administration of heparin.

After the usual operation for the division of adhesions, which is performed with as little additional trauma to the peritoneum as possible, and after complete hemostasis of the peritoneum, preferably obtained by ligature, the first step in the introduction of heparin can be taken.

A small stab wound is made through the wall of the abdomen near the area of the greatest mass of adhesions. Through this a no. 24 Pezzar catheter is threaded from within out and pulled up snugly against the anterior peritoneum. The abdominal wound is then closed, again with particular care to preserve hemostasis. After the dressings are applied, 10,000 units of heparin² in 300 cc. of physiologic solution of sodium chloride is allowed to run by gravity into the peritoneal cavity through the catheter. The catheter is then clamped, and the patient is returned to the ward.

At the end of twelve hours and after proper study, 5,000 units of heparin is instilled through the catheter in 300 cc. of physiologic solution of sodium chloride, and the same amount is given in the same manner and with the same precautions at twelve hour intervals for five additional doses, making a total of 40,000 units administered over three and one-half days. Experiments with animals^{1b} have indicated the necessity of continuing treatment for at least three days if the maximum effect is to be expected.

2. The heparin used in all but 2 of the cases to be reported is the product prepared by the Connaught Laboratories of the University of Toronto for clinical intravascular use. In recent months we have been furnished liquaemin through the courtesy of Hoffmann-Laroche, Inc. In a large number of laboratory trials this has been found to compare favorably with the heparin of the Connaught Laboratories in regard to both effectiveness and nontoxicity. We believe liquaemin is safe for clinical trial in the peritoneum; this is indicated by a recent report (Lam, C. R.: Heparin Administration: Methods and Results in Thirty Cases, *Ann. Surg.* **113**:1085-1086, 1941) on its successful use in the treatment of intravascular conditions. We have had no personal experience with any other brands of heparin.

Six hours after the last administration of heparin the stylet of the Pezzar catheter is introduced; the catheter is withdrawn, and the stab wound is left to heal. This interval is chosen in order to run no risk of bleeding from the vessels in the stab wound, which might be opened by the withdrawal of the catheter during the period of prolonged blood coagulation time.

If during any postadministration period the ordinary clinical signs of hemorrhage are noted, prompt treatment is indicated. This consists of discontinuance of any further administration of heparin together with immediate massive blood transfusion. Experimental studies in other laboratories³ showed an immediate neutralization of the action of heparin in the blood by protamine. Evans⁴ suggested the clinical use of protamine zinc insulin as an easily available form of protamine, to be covered of course with the proper amount of dextrose to protect the patient from acute hypoglycemia. No reports of the use of this method in the human being have been found. It seems reasonable to expect that in most cases bleeding due to intraperitoneal heparinization can be controlled by transfusion alone since the blood coagulation time is only slightly and transiently elevated.

REPORT OF CASES⁵

CASE 1.—W. W., a Negro man 44 years of age, was admitted to the University of Virginia Hospital in January 1939; the diagnosis was acute appendicitis with abscess of one week's duration. With conservative treatment the palpable mass disappeared, and the patient became afebrile. He was discharged on the eighth day after admission with instructions to return for interval appendectomy.

He was readmitted in March 1940 for this procedure; he presented no history of abdominal complaints during the thirteen month interval.

With the patient under spinal anesthesia, the appendix was removed, and a large number of thick adhesions in the region of the cecum were divided.

Before closing the peritoneal layer, 1,000 units of heparin in 300 cc. of physiologic solution of sodium chloride was placed in the peritoneal cavity. No further use of heparin was made in this case.

The postoperative course was smooth except for a somewhat persistent distention which lasted about four days; this was relieved by gastric suction. The highest blood coagulation time was twelve minutes. There was no evidence of intraperitoneal hemorrhage. The patient was discharged on the eighth postoperative day in excellent condition.

3. Chargaff, E., and Olson, K. B.: Studies on the Chemistry of Blood Coagulation: VI. Studies on the Action of Heparin and Other Anticoagulants; the Influence of Protamine on the Anticoagulant Effect in Vivo, *J. Biol. Chem.* **122**:153-167, 1937.

4. Evans, E. V.: The Clinical Use of Heparin in Thrombosis, *Virginia M. Monthly* **68**:200-203, 1941.

5. Of the 14 cases reported, 7 are from the University of Virginia Hospital, and the remaining 7 are from other clinics.

This was the first tentative use of heparin in the peritoneal cavity. We would not now feel justified in using heparin in such a case. Further, it was given in an amount which, as indicated by later experimental work, is probably inadequate.

CASE 2.—F. R., a Negro man 34 years of age, was first admitted to the University of Virginia Hospital on Oct. 19, 1940. Four years previously he had had an appendectomy performed elsewhere; this had been followed by drainage from the incision for twelve days. On admission he presented a typical picture of intestinal obstruction; this was treated by immediate surgical operation. In addition to an obstructing band in the region of the distal part of the ileum, exploratory operation revealed numerous other adhesions in the right lower quadrant; these were not divided. Convalescence was entirely satisfactory, and the patient was discharged on the thirteenth postoperative day.

He was readmitted four weeks later with another attack of intestinal obstruction of thirty-four hours' duration. Immediate laparotomy was carried out with the patient under spinal anesthesia. Obstruction was found to be due to a fine adhesion between the mesentery and the small bowel. After division of the band the obstruction was relieved. Eleven additional adhesions between loops of the ileum were also divided.

At and after this second operation, heparin was administered according to the technic already described. After operation the highest blood coagulation time was six minutes. At no time were there clinical symptoms or signs of intra-abdominal hemorrhage. The postoperative course was entirely smooth, and the patient was discharged on the thirteenth postoperative day. He was last seen on March 12, 1941; at that time there was no evidence of intestinal obstruction.

This patient was operated on under what we consider sufficient indications and was properly followed after operation.

CASE 3.—A. M., a Negro woman 51 years of age, was first admitted to the University of Virginia Hospital in 1936 and was discharged with a diagnosis of subsiding acute appendicitis. She returned one month later for appendectomy. Numerous adhesions were found in the region of the cecum; these were not disturbed except in so far as the removal of the appendix necessitated their division.

After more than five years of good health, she was admitted for the third time on Nov. 14, 1940 with a typical history of intestinal obstruction of three days' duration. With the patient under general anesthesia, an immediate operation was performed. In addition to two definitely obstructing adhesions others were found uniting the small bowel to itself, to the mesentery and to the large bowel; in all there were about fifteen. The thicker adhesions were divided after double ligation, and the others were divided by sharp dissection; coagulation of the divided ends was done with the high frequency current. The abdominal cavity was entirely dry on closure.

Heparin was given according to the standard technic. The postoperative course gave no indication of intraperitoneal hemorrhage and was altogether uncomplicated. The highest blood coagulation time was less than eight minutes. The patient was discharged in excellent condition on the fourteenth postoperative day.

She was readmitted about three weeks later with obscure abdominal pain in the right flank. Neither the history nor the physical examination nor the roentgen examination suggested intestinal obstruction. During a hospital stay of four days, the symptoms entirely disappeared, and she was discharged. She returned two

months later to the outpatient clinic, reporting that she had had no complaints in the meantime. Examination at this time showed her to be normal.

In this case the use of heparin after a first attack of intestinal obstruction from adhesions is illustrated. If the patient's condition will permit the complete separation of all accessible adhesions, the use of heparin in such a case may be justified.

CASE 4.—C. W., a white man 53 years of age, was first admitted to the University of Virginia Hospital in May 1936. At that time he had a partial intestinal obstruction for which he was treated conservatively with recovery. He had undergone appendectomy twenty-six years previously, and this had been followed by drainage from the wound.

He was well until three days before his second admission on Feb. 11, 1941 with a typical attack of acute intestinal obstruction. After dehydration had been corrected, operation was performed with the patient under spinal anesthesia. There were several adhesions between loops of the small bowel and between the small bowel and the scar of the previous operation. Division of the latter resulted in the release of the obstruction. All other adhesions were divided. Where ligatures were not easily applied, the bleeding points were coagulated with the high frequency current.

Heparin was administered according to the standard technic. The patient showed no evidence of intraperitoneal hemorrhage and experienced a smooth postoperative course except for a brief period of bronchopneumonia which was treated with sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and a superficial wound infection which was practically healed on discharge. The highest blood coagulation time was seven minutes. He left the hospital well on the thirteenth postoperative day.

This is another case in which sufficient indications for the use of heparin were present and in which the postoperative observation was adequate.

CASE 5.—E. H. S., a white man of 60 years, was admitted to the University of Virginia Hospital in 1934 with a history of acute abdominal disease persisting for ten days. There was obstruction of the rectosigmoid due to an inflammatory mass resulting from acute appendicitis. The mass was drained, and a lateral transverse colostomy was performed. After subsidence of the inflammatory process, the colostomy was closed; this left a hernia about 3 cm. in diameter. After this episode, the patient had occasional attacks which suggested partial intestinal obstruction and which were relieved spontaneously or by the use of enemas.

The patient was again admitted on May 19, 1941 with an attack of intestinal obstruction of twelve hours' duration. Relief was obtained with an enema. Within twenty-four hours a much more severe attack occurred which could not be relieved by enema, and operation was advised. On opening the abdomen with the patient under spinal anesthesia, many adhesions were observed throughout the abdominal cavity, including a band which was producing almost complete obstruction of the ileum. After this was divided, numerous other adhesions were separated, and bleeding was controlled by electrocoagulation. Appendectomy was then carried out. In the area of the hernia, no adhesions were disturbed.

Heparin was administered according to the standard technic. There were no signs of intraperitoneal hemorrhage, and the postoperative course was entirely

smooth. The highest blood coagulation time was five minutes. The patient was discharged in good condition on the fourteenth postoperative day.

This patient was advised to enter the hospital for the repair of his hernia within a few weeks after discharge; this would offer the opportunity to check on the effectiveness of heparin treatment in a single case.

CASE 6.—In 1937, A. B., a Negro woman 34 years of age, had undergone laparotomy in which the following procedures were carried out: supravaginal hysterectomy, right salpingo-oophorectomy, left salpingectomy and appendectomy. The postoperative course had been satisfactory.

She was admitted to the hospital on May 5, 1941 with a history of intestinal obstruction persisting for twelve hours. She was immediately placed under spinal anesthesia and operated on. A volvulus in the small bowel was exposed; this was apparently due to peritoneal adhesions. Resection of 2 feet (61 cm.) of the ileum was carried out with end to end anastomosis. The patient made a satisfactory recovery and was discharged on the thirteenth day after operation in excellent condition.

She was readmitted to the hospital on the following day, suffering from a definite syndrome of intestinal obstruction. She was treated conservatively for slightly over twenty-four hours, with temporary relief. At the end of that period, however, it was obvious that obstruction was continuing, and operation was therefore advised.

The abdomen was opened with the patient under spinal anesthesia. Considerable dilatation of the bowel was noted above a point of obstruction 10 cm. proximal to the site of anastomosis, caused by angulation of the bowel from a string adhesion. Division of the latter resulted in relief of the obstruction. Rather extensive separation of the adhesions followed and was associated with marked and persistent oozing from the granulation tissue that had formed after the operation two weeks before. The abdomen was apparently dry on closure, but hemostasis required extensive electrocoagulation.

Heparin was administered according to the standard technic at the time of operation. The first and second postoperative doses also were given. On the morning of the second postoperative day, the patient suddenly went into shock and died. The highest blood coagulation time was seven minutes. On account of an unfortunate oversight, the usual and essential postoperative studies of the red blood cells, the hemoglobin and the blood pressure were omitted. The only hint of impending disaster was an elevation of the pulse rate to 130 during the afternoon of the first postoperative day, associated with an elevation of temperature. This was ascribed to the common postoperative reaction after so extensive a procedure. No transfusion was given.

Autopsy revealed a large amount of fluid blood in the peritoneum, containing large clots; other observations were not related to the patient's death. The exact source of hemorrhage could not be determined.

In this case occurred the only death known to have followed the intraperitoneal use of heparin. In retrospect it is believed that the administration of heparin was definitely contraindicated in the presence of the extensive oozing from subacute inflammatory tissue, which was controlled with difficulty. It is also obvious that the patient had entirely inadequate postoperative observation. In view of the relatively slight elevation of the blood coagulation time, there is every reason to think

that one or two massive transfusions would have saved her life if the diagnosis of intraperitoneal hemorrhage had been made. This case will be further discussed later.

CASE 7.—O. S., a Negro man 65 years of age, was admitted to the University of Virginia Hospital on March 19, 1941 with a diagnosis of acute intestinal obstruction of thirty-six hours' duration without previous abdominal complaint. Immediate exploratory operation revealed numerous adhesions in the region of the appendix with fixation of one loop to the posterior abdominal wall. Since this was the first attack, heparin was not used. The patient was discharged from the hospital on the twelfth day after an entirely smooth convalescence.

He returned to the hospital on July 2 with recurrent obstruction. After four hours of medical treatment, operation revealed apparently more adhesions than had been present at the first procedure. About ten loops of bowel were involved. After complete freeing of adhesions and careful hemostasis, the abdomen was closed, and heparin was administered by the standard technic.

During the first twelve hours after operation the pulse rate rose to 130, and the systolic blood pressure dropped from 140 to 105. During this time the erythrocyte count and the hemoglobin content remained stationary at the preoperative level. The coagulation time during this period rose from three to five and one-quarter minutes. After the second dose of heparin, twelve hours after operation, the systolic blood pressure remained in the neighborhood of 125, with a slight drop seven hours later. During this period the red blood cell count had dropped from 5,200,000 to 4,000,000 and the hemoglobin content from 87 to 70 per cent. The third dose of heparin was therefore not given. Except for moderate ileus, the patient did well for the next two days. On July 5, however, it was found that the erythrocyte count had dropped to 2,500,000 and the hemoglobin content to 58 per cent. The patient was therefore given a transfusion; two more transfusions were given before discharge which occurred on the fourteenth day with the patient in excellent condition.

Although it is possible that the oozing continued for forty-eight hours after the last administration of heparin, it does not seem probable in the face of a normal coagulation time. Furthermore, no blood appeared in the inlying catheter, and the highest icteric index measured on several postoperative days up to the tenth was 11.

The case illustrates the proper management in cases of suspected intra-abdominal hemorrhage.

CASE 8.—Miss G., a white woman aged 40, was operated on by Dr. Warfield M. Firor at Johns Hopkins Hospital, Baltimore, on July 15, 1940. She had already undergone numerous operations with the division of extensive adhesions.

At the last operation many adhesions around the sigmoid and the cecum were divided without bleeding. A small catheter was inserted through a stab wound, and 10,000 units of heparin in 100 cc. of physiologic solution of sodium chloride was given at the close of the operation. This dose was repeated at twelve, thirty-six and forty-eight hours after operation. Six hours after operation there was a pinkish discharge around the tube, and subsequently a small hematoma developed in the wound. Otherwise the postoperative course was smooth without further evidence of bleeding. The bleeding time and the blood coagulation time remained within normal limits. The patient was free from symptoms of intestinal obstruction for at least six months after operation.

CASE 9.—B. K., a white woman 45 years of age, was operated on by Dr. James C. Owings at the Baltimore City Hospitals on Aug. 23, 1940. She had undergone six operations between the ages of 10 and 28 years: (1) at 10 years, operation on the left hip for tuberculous osteomyelitis; (2) at 14 years, appendectomy for ruptured appendix; (3) at 15 years, laparotomy, thought by the patient to have been performed for tuberculosis; (4) at 20 years, laparotomy for intestinal obstruction; (5) at 27 years, nephrostomy; (6) at 28 years, laparotomy with bilateral salpingo-oophorectomy.

Beginning in 1938, she experienced repeated attacks of constipation; relief was obtained from cathartics. On Feb. 3, 1940 she entered the Baltimore City Hospitals with acute intestinal obstruction, which was partially relieved by conservative treatment. Later operation revealed numerous dense adhesions which were extensively divided. Her postoperative course was satisfactory, and she was discharged on the seventeenth postoperative day.

She was readmitted to the hospital on August 9, with recurrent intestinal obstruction. After a period of conservative treatment, laparotomy was again performed on August 23. The entire gastrointestinal tract was involved in dense adhesions. These were completely separated from the level of the stomach to the pelvic diaphragm.

At the close of the operation a Carrel tube with multiple openings in its central portion was inserted into the peritoneal cavity with ends projecting from the upper and lower angles of the wound. Before the patient left the operating room, 15,000 units of heparin in 500 cc. of physiologic solution of sodium chloride was injected through the tube into the peritoneum.

Twenty-four hours after operation the patient went into shock and for two days had a stormy postoperative course, the cause of which was not specifically determined. Laboratory studies during the first postoperative day showed a highest blood coagulation time of three and one-half minutes, a hemoglobin content of 105 per cent and a red blood cell count of 4,500,000. No more heparin was given.

After recovery from shock, the patient followed a satisfactory course for a period of six days; after this she became febrile. Two and one-half weeks later, a pelvic abscess was drained by posterior colpotomy. At this time she had also an infected abdominal wound, which was draining when she was discharged on October 13. This area was reopened when she returned to the hospital on October 29. She was discharged on December 20, and on March 11, 1941 she still presented a small sinus. There were no complaints of intraperitoneal origin.

This is definitely the type of case in which the use of heparin is indicated. It is necessary to point out, however, that in this instance neither the Connaught heparin nor liquaemin was employed. A domestic product was used which has given unfavorable reactions in laboratory experimentation. In view of the evidence of blood concentration during the first postoperative day, it is not believed that the unfavorable reaction was due to hemorrhage.

CASE 10.—A white woman 60 years of age was operated on by Dr. Cecil F. Freed at the Reading Hospital, Reading, Pa., on Dec. 14, 1940. She had undergone nine previous operations, mostly for repeated attacks of intestinal obstruction due to adhesions. Dr. Freed had performed two additional operations which required extensive separation of adhesions.

At a third operation, heparin was employed according to the standard technic with the exception of the use of two Pezzar catheters, one on each side of the

abdominal incision. The patient had an entirely smooth postoperative course and about one month later was free of symptoms.

CASE 11.—An adult woman was operated on by Dr. Cecil F. Freed at the Reading Hospital on Dec. 14, 1940. This patient had undergone cholecystectomy one year previously and was admitted to the Reading Hospital with pain and vomiting. After separation of the adhesions, heparin was used according to the standard technic. Her postoperative course was entirely smooth.

CASE 12.—L. M., a white woman 42 years of age, was operated on at St. Elizabeth's Hospital, Richmond, Va., by Dr. Guy W. Horsley on April 10, 1941. In 1935 the patient had undergone excision of the left ovary and resection of a portion of the ileum for endometriosis. In April 1940 she was operated on for intestinal obstruction due to volvulus. Twenty-eight centimeters of the ileum was resected. On admission in April 1941, a diagnosis of intestinal obstruction was made and immediate operation carried out.

An adhesive band from the mesentery to the cecum obstructing the small bowel and several other string adhesions were divided. Ten thousand units of heparin in 100 cc. of physiologic solution of sodium chloride was injected into the peritoneal cavity before closure of the wound. No more heparin was used. The patient had an entirely smooth convalescence without evidence of intraperitoneal hemorrhage and was discharged on the twenty-first postoperative day.

CASE 13.—W. E. H., a white woman 46 years of age, was operated on at St. Elizabeth's Hospital by Dr. J. Shelton Horsley on May 15, 1941. In 1932 she had undergone bilateral salpingectomy and excision of the right ovary elsewhere. After these procedures a painful ventral hernia developed. At a recent operation multiple peritoneal adhesions were separated; the right ovary was removed, and the hernia was repaired. A small catheter was passed through a stab wound in the right flank. Ten thousand units of heparin was injected into the abdominal cavity through the catheter one hour after operation, and 5,000 units was given in 500 cc. of physiologic solution of sodium chloride at twelve hour intervals for four doses; the total administration of heparin was 30,000 units. There were no evidences of intraperitoneal hemorrhage, and the postoperative course was entirely smooth. After the last injection, the patient complained of considerable abdominal pain.

This is the only case of discomfort as a result of postoperative instillation of heparin which has been reported to us. In our own experience the procedure has been entirely painless.

CASE 14.—V. B., a white woman 32 years of age, was operated on at St. Elizabeth's Hospital by Dr. Guy W. Horsley on July 8, 1941. Two years before she had undergone an operation elsewhere for a chocolate cyst of the right ovary. The symptoms suggested recurrence. At operation numerous adhesions were observed. The most important of these adhesions had drawn the cecum over the upper surface of the broad ligament. All adhesions were divided, and the raw surfaces peritonealized as far as possible. Five thousand units of heparin (liquaemin, Hoffmann-Laroche) were given once daily for three days through an inlying catheter. The patient had an entirely smooth recovery.

COMMENT

In 11 of the 14 cases of intraperitoneal heparinization herein reported (table) there was no evident effect on the postoperative course from

the administration of the drug except a transient elevation of the blood coagulation time (chart). The actual effect of the procedure on the reformation of divided adhesions is not known in any case. In 1 case there was a severe reaction to heparin of a brand now known to be toxic; in this case there was no evidence of bleeding, and recovery ensued. One patient died of intraperitoneal hemorrhage. In 1 case hemorrhage was suspected but not demonstrated; administration of

Data on Fourteen Cases in Which Intraperitoneal Adhesions Were Treated with Heparin

Case; Race	Sex and Age	Hospital or Surgeon	Previous Laparot- omies	Previous Attacks of Obstruc- tion	Heparin Product Used	Technic of Treat- ment	Post- operative Course
1 Negro	M 44	University of Virginia	0	0	Connaught	Modified	Slight ileus
2 Negro	M 34	University of Virginia	2	1	Connaught	Standard	Smooth
3 Negro	F 51	University of Virginia	1	0	Connaught	Standard	Smooth
4 White	M 53	University of Virginia	1	1	Connaught	Standard	Smooth *
5 White	M 60	University of Virginia	2	1	Connaught	Standard	Smooth
6 Negro	F 34	University of Virginia	2	1	Connaught	Standard	Died from hemorrhage (see text)
7 Negro	M 65	University of Virginia	1	1	Connaught	Modified	Symptoms suggested hemorrhage
8 White	F 40	F. M. Floror	Numer- ous	Several	Connaught	Modified	Smooth (slight wound hemorrhage)
9 White	F 45	J. C. Owings	4	2	Toxic brand	Modified	Severe toxic (?) reaction
10 White	F 60	C. F. Freed	11	Numerous	Connaught	Standard	Smooth
11 White	F Adult	C. F. Freed	1	?	Connaught	Standard	Smooth
12 White	F 42	G. W. Horsley	2	1	Connaught	Modified	Smooth
13 White	F 46	J. S. Horsley	1	?	Connaught	Modified	Smooth
14 White	F 32	G. W. Horsley	1	?	Liquaemin	Modified	Smooth

* Patient had a brief attack of bronchopneumonia and a superficial wound infection.

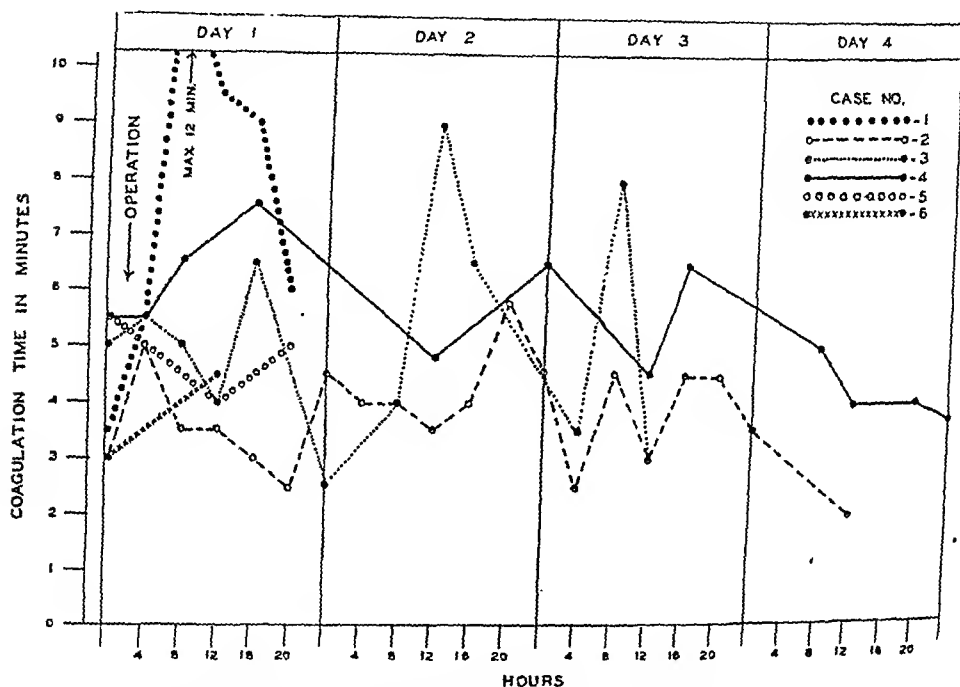
heparin was discontinued, transfusions were given, and the patient recovered.

In 11 of the cases there were no other complications worthy of note. There was apparently no greater incidence or degree of ileus than would ordinarily occur in a corresponding group of cases of obstruction treated without heparin. In 2 cases there were minor abnormalities in the healing of the wound. There was no apparent increase in average postoperative temperature readings and pulse rates. Postoperative discomfort was not increased.

As already stated, the single death can be blamed directly on poor judgment in selecting the case and on inadequate postoperative obser-

vation. If a tragedy in the use of this new method was destined to occur, it is fortunate that it occurred at the University of Virginia Hospital, where laboratory appraisal of the danger had already been made, and it is doubly fortunate that it occurred before the method was presented for clinical use. We have learned two lessons from this death.

The first and more obvious lesson is that care must be exercised to use heparin only in an unequivocally dry abdomen in which there has been no great difficulty in controlling oozing. This criterion will automatically exclude cases of recent laparotomy (such as case 6) in which granulation tissue is present.



Blood coagulation times after intraperitoneal heparinization in 6 cases of the University of Virginia Hospital series.

The second lesson is that no relaxation of vigilance in postoperative observation is permissible. Hemorrhage will remain the real hazard of the method; and possible hemorrhage must be foreseen in every case. This means that no matter what happy experiences may be had by the surgeons of any institution in 50 or 100 cases of intraperitoneal heparinization, those surgeons must not fail to follow the postoperative course of the next case with the same scrupulous care as they used in the first.

If these precautions are observed, we believe that the method is relatively safe for the type of patient who definitely needs protection from possible future intestinal obstruction. Until the actual effectiveness of the method in the human being is known, this opinion cannot be more than tentative. If definite benefit can later be shown in a large number of cases by a reduction in the number of intraperitoneal adhe-

sions, which would clearly diminish the chance of obstruction, then the choice between the risk of hemorrhage and the risk of later obstruction can be made on a firmer basis. Hemorrhage may, of course, occur in some cases, but there is slight reason that such hemorrhage need be fatal if detected early and treated adequately.

In the meantime, the method is proposed for clinical use in an entirely experimental and tentative way. We are planning to continue its use in the University of Virginia Hospital as long as properly selected patients, properly treated, continue to present uncomplicated postoperative courses.

In the presentation of a potentially dangerous method of treatment it is felt that a clearinghouse of information in regard to its application is important. We should therefore be grateful for immediate notification of any untoward experiences and for an occasional brief summary of successful use. We plan no further reports of cases from other clinics.

One warning, hardly necessary for experienced surgeons, must be issued. The object of an operation for acute intestinal obstruction is the cure of the acute attack. It is sound surgical treatment to combine no other intra-abdominal procedure, even an appendectomy, with the release of an offending band or bands. The surgeon must not yield to the temptation to add the burden of extensive separation of nonoffending adhesions in the sick patient because a possibly effective method of preventing future obstruction is at hand. If distention can be relieved by conservative measures, the possibility of widespread division of adhesions is increased. If distention cannot be relieved by conservative measures, it may be better in some cases to divide the obstructing band and to advise operation several weeks later for interval division of adhesions and heparinization. In cases in which there have been repeated attacks of obstruction, it may be sound not to wait for a fresh attack.

SUMMARY AND CONCLUSIONS

The indications, contraindications and technic of intraperitoneal heparinization in the human being for the prevention of the reformation of adhesions are presented and 14 cases are reported. In these cases there was one death. The single death was due to bad selection of the case and inadequate hospital observation.

Hemorrhage will remain a potential hazard in the application of the method described.

The method should not be applied if oozing is difficult to control or if there is granulation tissue present. Postoperative observation must be careful and continuous. With these precautions, the method is believed sufficiently safe to warrant further clinical trial.

No data on the effectiveness of the method in preventing adhesions in the human being are presented.

MULTIPLE MYELOMA, WITH SPECIAL REFERENCE TO SOFT TISSUE METASTASIS

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In 1928, Ewing¹ defined multiple myeloma as

. . . a specific malignant tumor of the bone marrow arising probably from a single cell-type and characterized chiefly by multiple foci of origin, a uniform and specific structure composed of plasma cells or their derivatives, rare metastases, albumosuria and fatal termination.

Vance,² considering the disease more from the clinical than from the pathologic standpoint, described multiple myeloma as characterized by

. . . multiple primary tumors of the bone marrow, occurring, for the most part, in elderly individuals, and manifested during life by deep-seated pain in the bones, characteristic deformities of the skeleton, spontaneous fractures in many bones of the body, severe secondary anemia, and emaciation.

Geschickter and Copeland³ emphasized that the

. . . disease not only produces extensive involvement of the skeleton, but the systemic manifestations are particularly widespread and that changes in the central nervous system, the thorax, the lungs, the kidneys and in the blood picture are frequently prominent features.

These authors further stated that "a careful pathologic study shows that all of these various phases in the symptomatology and physical findings are secondary to the lesions originating in the bones."

Others look on the disease as being a systemic anomaly of the hemopoietic apparatus rather than a true tumor and as having a definite relation to leukemia and aleukemia.⁴

Slavens⁵ defined the disease as

. . . a primary malignant tumor of bone marrow characterized by multiple foci in long and flat bones of the skeleton and usually associated with anemia, Bence Jones proteinuria, rare metastasis and a fatal termination.

From the Department of Surgery of Albany Hospital and Albany Medical College.

1. Ewing, J., cited by Jackson, Parker and Bethea.⁴¹

2. Vance, B. M.: *Am. J. M. Sc.* **152**:711-712 (Nov.) 1916.

3. Geschickter, C. F., and Copeland, M. M.: *Tumors of Bone*, revised ed., New York, American Journal of Cancer, 1936, pp. 441-488.

4. Barker, L. F.: *M. Clin. North America* **16**:1019-1027 (March) 1933.

5. Slavens, J. J.: *Multiple Myeloma in Child*, *Am. J. Dis. Child.* **47**:821-835 (April) 1934.

Historically, five names are constantly associated with this disease: Bence Jones, Watson, McIntyre, von Rustizky and Kahler. Credit must be given also to Dalrymple, who gave the first microscopic description of this condition, which he had observed in two affected ribs.

On April 22, 1847, Henry Bence Jones⁶ read the following words to his confrères of the Royal Society of London:

On the first of November, 1845, I received from Doctor Watson the following note, with a test tube containing a thick, yellow, semi-solid substance: The tube contains urine of very high specific gravity; when boiled it becomes highly opaque; on the addition of nitric acid it effervesces, assumes a reddish hue, becomes quite clear, but as it cools, assumes the consistence and appearance which you see: heat relieves it. What is it?

A few hours afterward, a specimen of the same patient's urine was sent to Bence Jones by McIntyre, who had been in attendance with Watson. McIntyre apparently noted the same phenomena as Watson. This was the beginning of the recognition of Bence Jones protein bodies as an occasional accompaniment of the then so-called mollities ossium.

Bence Jones began to make extensive studies and to set up hypothetical conclusions about the relation between the presence of these bodies and the disease mollities ossium. One of his conclusions was as follows: "So far as the albumin is concerned, each ounce of urine passed was equivalent to an ounce of blood lost."

Subsequently, McIntyre reported the first case of multiple myeloma to be recorded in the literature.

The term "myeloma" was introduced in 1873 by von Rustizky, who recognized the condition as a special disease of the bone marrow although in his case Bence Jones protein was not present in the urine.

In 1889, Kahler gave an excellent description of the disease, including as one of the characteristics the excretion of Bence Jones protein. However, it was not until 1897 and 1898 that Bozzolo in Italy awakened interest in this disease, and contributions including case histories of the disease soon followed.⁷

It was not until 1928 that Geschickter and Copeland⁸ analyzed a series of 425 cases including those cited in the literature since 1845 and 13 cases of their own. The authors cited Martiri and Wallgren as contributing views on the subject (1915 and 1920, respectively).

CAUSATION

The disease is essentially one that occurs in the sixth decade of life with, according to Geschickter and Copeland,⁸ the peak of incidence

6. Jones, H. B.: *Phil. Tr. Roy. Soc. London* **138**:55-62, 1848.

7. Bell, E. T.: *Am. J. Path.* **9**:393-415 (July) 1933.

8. Geschickter, C. F., and Copeland, M. M.: *Multiple Myeloma*, *Arch. Surg.* **16**:807-867 (April) 1928.

at 55. Its occurrence in children has been reported, but in most of the instances the diagnosis was not supported by microscopic examination. Berkheiser,⁹ however, in his discussion of multiple myeloma in children, stated that the disease occurs in this age group as well as in adults.

Slavens reported a case in which the patient was a child 4 years of age with the "characteristic findings and involvement of the spleen, liver and aortic lymph nodes," though "repeated urinalyses gave negative results except for a trace of albumin on several occasions." This case occurred at the Mayo Clinic in 1934.

Geschickter and Copeland⁸ mentioned trauma as present in 20 per cent of the cases; Oftedal¹⁰ expressed the belief that it plays an important role but that "it is often of such a trivial nature as scarcely to be noticed by the patient at the time of its occurrence."

Family history and infection are not considered as causative factors.

Geschickter and Copeland⁸ summed it up well when they stated:

. . . All in all, the etiologic obscurity that is attached to malignancy seems to extend in no less degree to multiple myeloma.

After exhaustive studies, Geschickter and Copeland⁸ came to the conclusion that multiple myeloma constitutes 0.03 per cent of all malignant growths. In 1918, Symmers¹¹ found only 3 cases in 4,000 post-mortem examinations at Bellevue Hospital. In 9,000 autopsies at the Johns Hopkins Hospital there were 4 cases, and in 400 cases of sarcoma of the bone at Johns Hopkins Hospital, multiple myeloma was present in only 3 per cent.

CHEMICAL FINDINGS

The following data represent the blood chemical findings in normal persons.

Serum albumin, 4.6 to 6.7 per cent¹²
 Globulin, 1.2 to 2.3 per cent¹²
 Total protein, 6.5 to 8.2 per cent¹²
 Calcium, 9 to 11 mg. per hundred cubic centimeters
 Phosphorus, 3.7 mg. per hundred cubic centimeters
 Sugar, 100 mg. per hundred cubic centimeters
 Creatinine, 1 to 2 mg. per hundred cubic centimeters
 Uric acid, 2 to 4 mg. per hundred cubic centimeters
 Urea, 12 to 15 mg. per hundred cubic centimeters
 Total nonprotein nitrogen, 25 to 30 mg. per hundred cubic centimeters

9. Berkheiser, E. J.: Multiple Myelomas of Children, Arch. Surg. 8:853-881 (May) 1924.

10. Oftedal, S.: Multiple Myeloma, J. A. M. A. 77:1547-1548 (Nov. 12) 1921.

11. Symmers, D.: Ann. Surg. 67:687-697 (June) 1918.

12. Rowe, A. H.: The Albumin and Globulin Content of Human Blood Serum, Arch. Int. Med. 18:455-473 (Oct.) 1916.

Phosphatase, 2.6 units per hundred milligrams with a wider increase of range in children.¹³

For many years calculations of serum calcium and of serum phosphorus have been made in diagnosing disease of bone because it has been known that in various disease conditions of the bones these determinations are affected. There is now a third determination, which is of the utmost importance, that of the serum phosphatase.

Mitchell and Crawford¹³ and Simmons¹⁴ have emphasized the importance of making a determination of this enzyme when diseases of bone are suspected, and Mitchell and Crawford add that

... sufficient evidence has been produced in the past few years to establish the importance of serum phosphatase in the differential diagnosis and prognosis of several bone diseases.

After reviewing the phosphatase determination in several hundred cases, these investigators have shown that in patients with Paget's disease, the serum phosphatase may rise to twenty or more times normal and that in patients with the osteoblastic types of osteogenic sarcoma, in those with metastatic carcinoma of the bone and especially in those with hyperparathyroidism the serum phosphatase is elevated but that in those with multiple myeloma it shows no increase.

Robison¹⁵ demonstrated that phosphatase, an enzyme extracted from bone and ossifying cartilage and from other tissues in smaller quantities, can liberate inorganic phosphorus by breaking down solutions of complex organic compounds of phosphorus, such as the glycerophosphates and the hexosephosphates. It is Robison's hypothesis that the phosphatase available in the cells of bone and ossifying cartilage reacts with the glycerophosphates or the hexosephosphates in the blood. By this means there is produced a local increase of inorganic phosphorus in the region of these cells. This increase of phosphorus alters the calcium-phosphorus equilibrium, and calcium phosphate is deposited. That the enzyme is present in bone and in the circulatory system was shown by Martland, Hansman and Robison¹⁶ and Roberts.¹⁷ The presence in the blood of the type of organic phosphorus compound that may be broken down by phosphatase was demonstrated by Kay and Robison in 1924.¹⁸

13. Mitchell, C. L., and Crawford, R. G.: *J. Bone & Joint Surg.* **19**:630-637 (July) 1937.

14. Simmons, C. C.: *Ann. Surg.* **102**:555-562 (Oct.) 1935.

15. Robison, R., and Soames, K. M.: *Biochem. J.* **18**:740-754, 1924.

16. Martland, M.; Hansman, F. S., and Robison, R.: *Biochem. J.* **18**:1152-1160, 1924.

17. Roberts, W. M.: *Brit. J. Exper. Path.* **11**:90-95 (April) 1930.

18. Kay, H. D., and Robison, R.: *Biochem. J.* **18**:755-764, 1924.

It has been shown by these and many other investigators that in any disease in which there is concomitant formation of large amounts of new or abnormal bone there will as a rule be an elevation in the serum phosphatase. They have pointed out that the determination of this enzyme can be of value in both the diagnosis and the prognosis in cases of bone tumor, osteitis fibrosa cystica, Paget's disease and other conditions involving bone.

However, it should be borne in mind that there is likewise a variation in the serum phosphatase activity of patients having jaundice or nephritis or receiving a high carbohydrate diet.¹³

Kay¹⁹ noted an increase in the plasma phosphatase of patients with osteitis fibrosa, osteitis deformans, active rickets and osteomalacia.

TABLE 1.—*Serum Calcium and Inorganic Phosphorus and Plasma Phosphatase in Various Conditions of the Bones (After Morris and Peden²¹)*

Disease	Serum Calcium	Serum Phosphorus	Plasma Phosphatase
Osteitis deformans (Paget's).....	N	N	++++
Generalized osteitis fibrocystica (Recklinghausen's)...	++	—	+++
Solitary bone cysts (single or multiple).....	N	N	N or +
Myeloma.....	N or +	N or +	N
Metastatic bone cancer.....	+	+	++
Osteogenic sarcoma.....	+	+	++
Other bone tumors.....	N	N	N
Rickets.....	N or —	—	++
Osteomalacia.....	N or —	—	++
Osteogenesis imperfecta.....	N	N	N or +
Senile osteoporosis.....	N or —	N	N

Bodansky and Jaffe²⁰ emphasized that a marked rise of plasma phosphatase does not necessarily accompany destruction of bone unless there is also present the formation of new bone or of osteoid tissue. In other words, the phosphatase is highest in cases in which there is excessive formation of abnormal osseous tissue. Morris and Peden²¹ recently conducted investigations of the significance of phosphatase findings in the diagnosis of various diseases. Their table on differential diagnosis is included in this paper as table 1.

The absence of chemical changes in the blood in cases of multiple myeloma is, as a rule, so outstanding compared with the changes in cases of other anomalies otherwise presenting many of the same symptoms that chemical examination must be considered of great importance in the differentiation of this disease from others. However, occasionally there

19. Kay, H. D.: J. Biol. Chem. 89:235-247 (Nov.) 1930.

20. Bodansky, A., and Jaffe, H. L.: Phosphatase Studies: Serum Phosphatase in Diseases of Bone; Interpretation and Significance, Arch. Int. Med. 54:88-110 (July) 1934.

21. Morris, N., and Peden, O. D.: Quart. J. Med. 6:211-230 (April) 1937.

is an increase in the globulin fraction in cases of this disease, and often there is an inversion of the globulin rates, but as Peters and Eisenman²² stated:

. . . Increases of globulin are found with infections, especially suppurative processes and ulcerative tuberculosis or syphilis; in connection with certain tumors, particularly myelomata; and in cirrhosis of the liver.

Cantarow²³ noted that at times there may be definite hypercalcemia in cases of multiple myeloma; this is demonstrated in a case in our series. However, hypercalcemia is not pathognomonic of the disease.

Hyperproteinemia is sometimes one of the most striking concomitants of this disease. The first case of true hyperproteinemia associated with multiple myeloma was reported by Perlzweig, Delrue and Geschickter.²⁴ Since that time reports of other cases have followed in rapid succession, and Sweigert²⁵ made the statement that the most striking examples of hyperproteinemia have been observed in cases of multiple myeloma, though reports of cases have been found in the literature of certain types of infection, notably kala-azar, of large tumors of the kidney and of other neoplasms in the diagnosis of which this symptom is of great importance. It must be remembered, however, that this symptom may not be present and that the total protein may be only slightly increased. As a general rule, however, hyperproteinemia should always be regarded with suspicion when it is present.

In 1933 Wintrobe and Buell²⁶ stated that in the reports of approximately 500 cases of multiple myeloma "abnormality in the blood plasma has been found only in 8 instances." They cited a case of their own in which hyperproteinemia was associated with multiple myeloma.

Reimann²⁷ reported a case of spontaneous rouleau formation of the red cells, which led to the discovery of marked hyperproteinemia. Foord²⁸ presented 4 cases of multiple myeloma in which there was profound autohemagglutination of the red cells and marked hyperproteinemia. In 2 of his cases there was uncontrollable prolongation

22. Peters, J. D., and Eisenman, A. J.: *Am. J. M. Sc.* **186**:808-833 (Dec.) 1933.

23. Cantarow, A.: *Am. J. M. Sc.* **189**:425-428 (March) 1935.

24. Perlzweig, W. A.; Delrue, G., and Geschickter, C. F.: *Hyperproteinemia Associated with Multiple Myelomas: Report of Unusual Case*, *J. A. M. A.* **90**:755-757 (March 10) 1928.

25. Sweigert, C. F.: *Am. J. M. Sc.* **190**:245-256 (Aug.) 1935.

26. Wintrobe, M. M., and Buell, M. V.: *Bull. Johns Hopkins Hosp.* **111**:156-165 (Feb.) 1933.

27. Reimann, H. A.: *Hyperproteinemia as Cause of Autohemoagglutination: Observations in Case of Myeloma*, *J. A. M. A.* **99**:1411-1414 (Oct. 22) 1932.

28. Foord, A. G.: *Ann. Int. Med.* **8**:1071-1089 (March) 1935.

of both bleeding and clotting time and an increased calcium content with little change in the platelet count. He further stated that the pronounced rouleau formation observed in the smears of the blood of 2 of the patients led to the procedures which terminated in making the final diagnosis of multiple myeloma. Schumacher, Williams and Coltrin²⁹ recently reported a case of plasma cell myeloma with an unusually high blood protein content, autohemagglutination, hemorrhage and renal insufficiency.

Hansen³⁰ reported 1 case in which there was hyperproteinemia due to an increase in pseudoglobulin. He assumed that functional disturbances in the cells of the bone marrow may be the underlying factor. He emphasized the fact that the Takata-Ora reaction may be positive in the disease, without apparent disturbances of the liver.

Decherd and Holland³¹ recently mentioned 2 cases of multiple myeloma. In 1 there were hypercalcemia and hyperglobulinemia with a greatly accelerated sedimentation rate; Bence Jones protein was found in large amounts. In the second case there were retention of nitrogen in the blood without elevation of blood pressure and hypercalcemia with normal phosphorus content. The authors said "An increase in blood proteins is uncommon, and when found should lead to suspicion of multiple myeloma."

In 1938, Feller and Fowler³² analyzed 52 cases of multiple myeloma with hyperproteinemia which they collected from the literature, and reported 3 of their own from a series of 10 cases of multiple myeloma.

Blood Viscosity: Albers³³ recently published his observations on the changes in the blood in 3 cases of multiple myeloma. He reported that in all 3 the viscosity was increased; in 2 the viscosity values surpassed "all hitherto observed values." In these 2 cases the globulin fraction of the serum was markedly increased; in the third case, which showed the least increase in viscosity, the globulin fraction was increased to only a minor degree. The viscosity did not decrease as the temperature increased but rather decreased "several times as much." This investigator attributes the increase in viscosity to the increase in the globulin content of the serum.

29. Schumacher, I. C.; Williams, O. O., and Coltrin, G. S.: *California & West. Med.* **47**:174-177 (Sept.) 1937.

30. Hansen, O. S.: *Multiple Myeloma*, *J. A. M. A.* **79**:2059-2061 (Dec. 16) 1922.

31. Decherd, G. M., Jr., and Holland, L.: *J. Trop. Med.* **41**:129-132 (April 16) 1938.

32. Feller, A. E., and Fowler, W. M.: *J. Lab. & Clin. Med.* **23**:369-372 (Jan.) 1938.

33. Albers, D.: *Ztschr. f. klin. Med.* **132**:705-828, 1937; abstracted, *J. A. M. A.* **110**:407 (Jan. 29) 1938.

BENCE JONES PROTEIN

According to Anders and Boston,³⁴ Bence Jones protein is a normal constituent of the spermatic secretion and may be found in the bone marrow in cases of myeloma. According to most investigators, it is present in approximately 65 per cent of all cases of multiple myeloma. At times, frequent tests must be made of the urine before it is found, but its absence in no way excludes the possibility of the presence of the disease. This test is easily performed by any laboratory worker, and the detection of these bodies in the urine is of such extreme importance as a diagnostic factor in cases in which there is a suspicion of obscure myeloma that it should be carried out as a routine procedure whenever the disease is suspected.

Jacobson³⁵ reported finding Bence Jones protein in the circulating blood of a patient with multiple myeloma associated with advanced nephritis.

There are cases on record, and many of them, in which the finding of Bence Jones protein was the first clue to the existence of multiple myeloma. However, before stressing too much the import of Bence Jones protein, one must remember that this protein is often present with Hodgkin's disease, malignant tumor of the bone, especially diffuse carcinomatosis, lymphogranulomatosis, myxedema,³⁶ leukemia, cirrhosis of the liver and sometimes extensive suppurative processes. In fact, Bloodgood³⁷ reported a case in which Bence Jones protein was present in the urine of a patient with typhoid osteomyelitis of a rib.

Cantarow emphasized that frequently failure to detect Bence Jones protein is probably due to the fact that its characteristic properties of precipitation at relatively low temperature and resolution at higher temperature are by no means invariably exhibited. He further stated that

... the relatively rapid and marked fluctuations in serum protein and serum calcium concentrations in patients with multiple myeloma and the variability of the several factors which determine the characteristic precipitation reactions of Bence-Jones protein emphasize the necessity for repeated studies in such cases.

GROSS OBSERVATIONS

Myeloma involves most frequently and extensively those bones with the greatest content of red marrow. Thus the vertebrae, the ribs, the sternum, the clavicles and the skull are the most commonly affected, while the long bones, which are relatively cortical, are as a rule not

34. Anders, J. M., and Boston, L. N.: *Lancet* 1:93-97 (Jan. 10) 1903.

35. Jacobson, V. C.: *J. Urol.* 1:167-178 (April) 1917.

36. Caylor, H. D., and Nickel, A. C.: *Ann. Surg.* 97:823-827 (June) 1933.

37. Bloodgood, J. C.: *Progressive Med.* 4:229, 1906.

involved. Any of the bones, however, may become involved in the pathologic process. Grossly, the shell of bone embracing the tumor is of parchment thinness; it cuts readily with a knife. The tumor is extremely vascular and is made up of gray-red or dark red material; it is friable and of a more or less gelatinous consistency. The tumor is definitely destructive of bone.

Wells³⁸ remarked that a myelomatous growth may take on the characteristics of a neoplasm of vascular origin, retaining no remnants of the original tumor in the entire bony mass. He made the assertion, to which Ewing subscribed, that many a tumor described as vascular endothelioma of the bone and, sometimes, as a bone aneurysm, is really myeloma.

KIDNEYS

Perla and Hutner³⁹ concluded from their study of the pathologic changes in the kidney in cases of multiple myeloma associated with Bence Jones albumosuria that the following changes are present:

. . . (1) a nephrosis specifically associated in some way with the Bence-Jones albumosuria and the myeloma; (2) arteriosclerosis of the kidney, an independent vascular disease of the kidneys, present in a milder or severer form in almost every instance . . . and (3) calcium deposits in the kidney tubules dependent on a destruction of bone and the release of large quantities of calcium in the blood.

Anatomically, the nephrosis is severe. Microscopically, the kidneys are contracted; there is extensive destruction of the tubules of the cortex and the medulla, with replacement by dense cellular fibrous tissue.

Perla and Hutner emphasized the importance of distinguishing the nephrosis of this disease from the idiopathic type. In multiple myeloma there are an absence of edema, an increase in the concentration of the nonprotein nitrogen in the serum and an inability to concentrate urine with a consequently low specific gravity of the urine.

Longcope⁴⁰ spoke of the occurrence in some instances of myeloid degeneration of the kidneys, the spleen and the liver.

James referred to the cells composing multiple myeloma as derived from the primary mesenchyma, *Wanderzellen*. He expressed the opinion that there is a definite relation between multiple myeloma and leukemia, aleukemia and other diseases of the lymphatic hemopoietic apparatus. Plasma cells are most prominent in the plasma cell type of multiple myeloma; in the myeloid type myeloblasts predominate. Extensive changes

38. Wells, H. G.: Relation of Multiple Vascular Tumors of Bone to Myeloma, *Arch. Surg.* 2:435-442 (May) 1921.

39. Perla, D., and Hutner, L.: *Am. J. Path.* 6:285-298 (May) 1930.

40. Longcope, W.: *Internat. Clin.* 2:91-97 (June) 1927.

are occasionally present in the liver, the spleen and the kidneys, though their occurrence is far from constant.

In many cases studies of the kidneys show an entirely normal structure; in others in which there is associated Bence Jones protein, albumosuria, nephrosis, arteriosclerosis and calcium deposits are present. Anatomically, nephrosis is severe; microscopically, there is extensive destruction of the tubules of the cortex and the medulla, with replacement by dense cellular fibroid tissue. Occasionally, pyelonephritis develops, resulting from compression of the spinal cord or from hypertrophy of the prostate.

Bell stated that the only direct effect of multiple myeloma on the kidneys is due to the formation of tubular casts of Bence Jones protein that obstruct and cause atrophy of the tubules. When large numbers of tubules are obstructed, extensive atrophy occurs, and renal insufficiency ensues.

Geschickter and Copeland³ mentioned the fact that in recent years multiple myeloma, instead of being regarded as a true tumor, is considered by many as a disease of the blood-forming apparatus related to aleukemia and leukemia. Jackson, Parker and Bethea⁴¹ use the terms "extraosseous" and "intraosseous plasmocytomata" but are hesitant to state whether true myeloma should be classed as an

... intrinsic disease of the bone marrow or as a disease of the hemopoietic system in general, capable of involving extra-osseous structures and possibly even arising in them. According to Barr and Bulger,⁴² who reviewed the writings of Beck and McCleary, of Ghon and Roman and of Piney, plasma cells have been demonstrated in the blood of patients with apparently typical multiple myeloma, and the spleen, the liver, the ribs, the sternum and the spine have been involved in cases of so-called plasma cell leukemia.

In 1936, Osgood and Hunter⁴³ reported a case of plasma cell leukemia. Patek and Castle⁴³ described another case and mentioned 11 previously reported. Reiter and Freeman⁴⁴ have summarized these cases as follows:

A study of all possible cases reveals that the distinction between the localized form of the disease (plasma cell myeloma) and the diffuse form (plasma cell leukemia) is not a sharp one and any attempted classification such as that of Piney and Riach,⁴³ which considers the intermediate groups, must be arbitrary. We believe that all may be fundamentally a manifestation of the same process; nevertheless, it is obvious that some cases have certain outstanding characteristics acceptable as truly leukemic, which others lack.

41. Jackson, H., Jr.; Parker, F., Jr., and Bethea, J. M.: *Am. J. M. Sc.* **181**: 169-180 (Feb.) 1931.

42. Barr, D. P., and Bulger, H. G.: *Am. J. M. Sc.* **179**: 449-476 (April) 1930.

43. Cited by Reiter and Freeman.⁴⁴

44. Reiter, B. R., and Freeman, J. T.: *Am. J. M. Sc.* **193**: 38-42 (Jan.) 1937.

Jackson, Parker and Bethea classified the plasma cell type of multiple myeloma as malignant lymphoma; they concluded

. . . that the disease in its classical form is largely limited to the bones does not militate against such a view when one considers the marked variation of the disease picture and the gradual manner in which the cases blend into each other.

Blatherwick⁴⁵ and Longcope found calcification in the liver, the spleen, the vessels of the heart, the lymph glands, the gastric mucosa and the kidneys; connective tissue was the main site of the deposits.

INVOLVEMENT OF THE SOFT TISSUES

In a monograph published seventeen years ago, Oftedal emphasized the importance of considering the multiple lesions found in the tissue as metastatic tumor rather than individual independent primary lesions of the blood-forming tissue, and he stated that "so far pulmonary metastasis has not been found."

Observers now more frequently record instances of involvement of the liver, the spleen, the lymph glands and the hemolymph glands, the cardiac muscle, the kidneys, the tonsils, the thyroids, the adrenal glands, the ovaries, the meninges and, less frequently, the pituitary gland, with tumor masses identical with those in the bone marrow.⁴⁶

It is conceded that the blood-forming tissues are the favorite sites.

That tumor cells are found lying within the blood vessels, at times diffusely distributed in the sinuses of the liver and in the capillaries of the kidneys indicates metastasis rather than independent growth.

In 1934, Flax⁴⁷ stated

. . . that while the individual tumors may be primary lesions, their distribution throughout the skeletal system lends all the clinical aspects of a widespread metastasis.

Wood and Lucké⁴⁸ reported large numbers of myeloma cells in the spleen and in the liver and expressed surprise that in view of the vascularity of the tumors and of the frequent presence of myeloma cells within the blood channels of the tumor these cells were not more often found in the circulating blood.

Gilmore⁴⁹ took a decided stand that multiple myeloma does not metastasize, although the "multiplicity of the lesions makes it appear to do so." He further stated that "pathologically, the disease does not

45. Blatherwick, N. R.: *Am. J. M. Sc.* **151**:432-436 (March) 1916.

46. Blackmar, M. L.: Personal communication to the authors, 1937.

47. Flax, N., cited by Graham,⁶⁰ 1934, pp. 97-98.

48. Wood, A. C., and Lucké, B.: *Ann. Surg.* **78**:14-25 (July) 1923.

49. Gilmore, M. E.: *Texas State J. Med.* **21**:358-362 (Oct.) 1925.

tend to extend locally" and that the "lesions remain confined to the bony system which is sorely damaged by the process."

In 1931, Jackson and Parker reported that in a series of cases of multiple myeloma

... extra-osseous involvement occurred in 2 out of 17 classical cases, and in one of the plasmomata primary in a lymph node.

Willis⁵⁰ was not willing to commit himself as to whether lesions of myelomatosis are metastatic in nature or multicentric in origin.

Shennan⁵¹ claimed that there are no true metastases of multiple myeloma. He said:

The disease is confined to the osseous system, and may affect the greater part of it. Cases of apparent metastasis, such as Hoffmann's (in liver), Lubarsch's (in mediastinum), Verebely's (in larynx), and Kahler's (in inguinal region and in infra-spinatus), have to be submitted to careful scrutiny, seeing that such "metastases" are occasionally capable of another explanation than that they are true secondary colonies the formation of which characterizes malignant tumour-growth. Verebely's case is of special interest. In it an apparent metastasis had taken place to the cricoid cartilage, but this and other laryngeal cartilages had undergone ossification, with development of marrow. As for the other cases, it must be remembered that islets of haematopoietic bone marrow have not infrequently been demonstrated in soft tissues and organs outside the bones, and if multiple myeloma be regarded as a disease especially attacking functioning "red" marrow, then in that disease all such marrow, whether within or outside the bones, must be liable to undergo the peculiar transformation described.

Still, even granting all this, we are not yet in a position either to affirm or deny that in rare cases myeloma may form true metastases in the soft tissues. The spleen, liver and lymph glands may become enlarged, congested, and beset with grey nodules and streaks, but these or similar changes occur in other diseases, and are not characteristic, and certainly not constantly remarked, in cases of multiple myeloma. As a matter of fact, when these organs show marked alterations in myeloma, an incorrect diagnosis may be suspected, or some intercurrent affection has obscured the issues. Nevertheless it must be recognized that competent observers have reported the presence in these organs of clusters of cells similar to those occurring in the local foci in the marrow.

Lubarsch⁵² corrects an error of Saltykow⁵³ and Menne,⁵⁴ who published reports of 1 of his cases of myeloma; they claimed that two myelomatous nodules found in the soft tissues of the mediastinum represented metastases. According to Lubarsch, these nodules were in reality the result of direct extension from a focus in the marrow of the sternum with which they were connected.

50. Willis, R. A.: *The Spread of Tumors in the Human Body*, London, J. & A. Churchill, 1934, p. 325.

51. Shennan, T.: *Edinburgh M. J.* **10**:321 and 414, 1913.

52. Lubarsch, O.: *Virchows Arch. f. path. Anat.* **184**:213-220, 1906.

53. Saltykow, S.: *Virchows Arch. f. path. Anat.* **173**:531-538, 1903.

54. Menne, E.: *Virchows Arch. f. path. Anat.* **183**:115-128, 1906.

He discussed also the various conceptions of myeloma and concluded that it is to be regarded not as true blastoma but as a systemic disease of the lymphatic-hemopoietic apparatus, closely related to leukemia.

He enumerated four forms: myeloma (myelocytoma), lymphocytoma, erythroblastoma and plasmacytoma. Multiple foci of involvement are explained by saying that the cells which are diseased are found in all these places in normal tissue, and hence the condition is not a primary tumor with multiple metastases but rather an outbreak of the disorder at various places in a single system. From this it follows that the soft tissues also may be involved, for plasma cells, myelocytes and erythroblasts are found in the soft tissues as well as in the bone marrow. The kidneys, the liver and the spleen are the soft tissues most often involved.

In reviewing the subject, Anders and Boston said, "Glandular enlargement is recorded in connexion with 15 per cent. of the cases, but in none of these did microscopic study show the growths of the glands to be identical with those developing from the bones."

Christian⁵⁵ gives a histologic comparison of 6 cases of myeloma. Of these, in only 1 was there involvement of the soft parts aside from direct extension. However, autopsy was not performed in all cases. In the case in question, in addition to multiple bone lesions, there was a non-sensitive movable tumor the size of an English walnut in the right axilla and two smaller masses on the right upper arm, apparently not attached to the bone. The microscopic description of the axillary node is as follows:

In a section . . . there are numerous areas of epithelioid cells some of which contain also giant cells and form very typical tubercles. Besides this the sinuses here and there in the lymph nodes are filled with cells of the identical type of those previously described as occurring in the tumor. In places it is a question whether these masses of tumor cells are in true lymphatics, or growing as masses in the structure of the lymph node itself. However, the suggestion is that the tumor is pretty well confined to the lymph channels, while in the tissue about there are lymphoid and plasma cells of the ordinary type with the possibility of an occasional tumor cell, but this latter is open to doubt.

Christian cited a case of Hoffmann,

. . . unique in that it is a characteristic myeloma with metastasis in the liver. Extension from bone to soft parts often occurs, but with the exception of Hoffmann's case and my Case III, metastasis is not reported.

Kaufmann⁵⁶ made the following statement:

The question of metastases is much argued: it is closely related to the question of whether the myelomas are hyperplasias or true tumors, whether the latter may appear from the former, and whether these tumors are benign or malignant. Nodular myeloma formation occasionally occurs in other organs, such as the

55. Christian, H. A.: *J. Exper. Med.* 9:325-351, 1907.

56. Kaufmann, E.: *Pathology*, translated by S. P. Reimann, P. Blatter, etc. Son & Co., 1929, vol. 2, p. 1217.

spleen, liver, kidneys, lymph nodes and others, and produces the picture of metastatic nodules. It is, however, probable, that these are not true metastases such as occur in malignant tumors, but merely an expression of a systemic disease of the hematopoietic apparatus.

A case was reported by Herrick and Hektoen,⁵⁷ the anatomic diagnosis in which was:

. . . Multiple tumors in the sternum, the ribs, the spine, the right clavicle, the left humerus, the right humerus, the left malar bone, the skull; invasion of the adjacent soft tissues and of the dura; tumors in the ovaries . . .

The ovaries were said to contain a few small tumors, of reddish color, firm in consistence and irregular in size and shape.

. . . Sections were made from most of the medullary tumors and from the growths in the ovaries. The structure is the same in all, and consists of round, lymphoid cells, with quite large nuclei arranged in a finely fibrillated, at times almost homogeneous matrix; in places they are very closely packed together, in other places more loosely. There are many blood-spaces of irregular size and shape found in the tumors, usually without any definite walls, the blood-mass being in direct relation with the surrounding wall of lymphomatous cells.

The authors mentioned also an article of Grawitz, describing

. . . a case of anemia following typhoid fever, in which round-celled sarcomatous tumors developed in the cranium, the vertebrae, the femora, the humeri, the bones of the legs, the right clavicle, the ribs, the sternum; there were also tumors in the liver, the right adrenal, and a disseminated involvement of the peritoneum.

Mention is also made of a case of Kahler's in which flattened, elevated masses appeared on the surfaces of the bones, particularly those of the ribs. At the end of six years there was marked kyphosis in the upper dorsal region of the spine and during the last year of life (the eighth year of the disease) the inguinal glands slowly enlarged. Microscopic examination revealed multiple development of a tissue with the characteristics of round cell sarcoma.

Horsch⁵⁸ recently noted that "tumors of the lymph nodes, spleen, or liver occasionally occur."

In our series of 5 cases, in all of which autopsy was performed, there was direct extension to the adjacent tissues in 1 case, the primary lesion being in the pubis (case 2). In case 3 there was definite metastasis to the myocardium, the retroperitoneum, the spleen, the liver, the adrenal glands, the ethmoidal sinus and the sella turcica. In case 4 there was definite metastasis to the lungs, the peritoneal lymph glands, the pancreas and the kidneys; in case 5 there was definite metastasis to the heart and to the spleen. (A description of the tissue will be given later.) In case 1 there was no evidence of either metastasis or extension.

57. Herrick, J. B., and Hektoen, L.: *M. News* 65:239-242, 1894.

58. Horsch, K., abstracted in Graham, E. A.: *Year Book of General Surgery*, Chicago, The Year Book Publishers, Inc., 1935, p. 136.

To us these observations are of extreme importance. We feel that our 4 cases supply evidence to support the opinion that multiple myeloma may in many cases metastasize or extend by direct invasion of the surrounding tissue. It is interesting to note that in case 4 there was metastasis to the lungs.

SYMPTOMS

The possibility of multiple myeloma is to be considered in diagnosing the condition of a patient presenting headache, backache or pains of obscure origin in the bones, especially if the patient is a man in the sixth decade of life.⁵⁹ The pain is made more intense by motion or pressure and is subject to remissions and acute exacerbations. However, it may be intermittent, severe, wandering or recurrent and may be fugitive and not intense.²¹ At times it may be quite bizarre and may be rheumatic in type.

The patient's attention may first be attracted to his illness by a sharp pain in the back or the thorax, brought on by sudden movement or muscular exertion. The attacks may be severe, the patient suffering for several days with "bone-breaking" pains in the lumbar and sacral regions or over the lower ribs. There may then be periods of intermittency and a so-called symptomatic period, which may last for several months. During the final stages of the disease, the pain reaches a climax, in which it attains its maximum intensity.

McConnell⁶⁰ first noticed severe precordial pains which radiated through the chest. Exertion made them worse, and they were followed by a sense of soreness felt all over but particularly through the abdominal and lumbar regions.

Spontaneous fractures are common and occur in about 62 per cent of all cases.³ With probably no other disease of the bone, if we except osteogenesis imperfecta, are fractures so common.

It is not uncommon to find bronchitis and emphysema.

Blood pressure readings are of importance according to some eminent clinicians, such as Hammond,⁶¹ who expressed the opinion that chronic nephritis with nonprotein nitrogen retention and a low blood pressure is typical of multiple myeloma. Other investigators have paid little attention to this finding, for Longcope, McConnell and others have described cases of their own in which the blood pressure has been as high as 190 systolic and 100 diastolic.

In 1937, Davison and Balser⁶² reported 12 cases of multiple myeloma with special reference to neural complications. In the majority of their

59. Gros, W.: *Deutsches Arch. f. klin. Med.* **177**:461-474, 1935; abstracted *Arch. Path.* **22**:562 (Oct.) 1936.

60. McConnell, G.: *Am. J. M. Sc.* **165**:184-195 (Feb.) 1923.

61. Cited by Geschickter and Copeland.⁸

62. Davison, C., and Balser, B. H.: *Myeloma and Its Neural Complications*. *Arch. Surg.* **35**:913-936 (Nov.) 1937.

cases in which lesions of the spinal cord were present the neurologic symptoms were produced by compression of the vessels of the spinal cord. They explained that a myelopathic process resulted from interference with the circulation. Herpes zoster was noted in a number of their cases; it was caused by direct compression of the spinal roots by the neoplasm.

It was interesting to note in this series of cases that in 1 case the myelomatous nodules of the cerebral dura and the skull interfered with the cerebral circulation and produced paranoic psychosis.

Of this series of 12 cases, in 6 of which autopsy was performed, there was involvement of the spinal cord, the spinal roots, the cerebral nerves or the brain. In 6 cases with signs of lesions of the spinal cord or the spinal roots, the neural structures were not removed.

There is such variation in the neurologic symptoms that we believe there is no definite symptom complex related to the peripheral or the central nervous system. Headaches, facial neuralgia and paraplegia, all may occur, depending on the involvement of the nerve roots and the stage of the disease.

Posture and deformities may play a most important part in the diagnosis. The patient often becomes shorter; the distance from the crest of the ilium to the shoulder is much reduced; the abdomen becomes protuberant; the chest becomes thick. In the anteroposterior plane, the patient may assume a most curious posture as he stoops. The knees are bent; the body is thrown in an abnormal position in order to keep balance; he bends over with difficulty and in so doing keeps his lumbar vertebrae fixed; he does not bend his spine.⁴⁰ Deformities may also occur from the presence of pathologic fractures.

Blood changes may show only anemia, though in most cases there is an increase in the lymphocytes, and the proportion of myelocytes often reaches 10 per cent.

PROGNOSIS

The average duration of life is two years,³ though cases are on record in which the patient lived for only a few months after the inception of symptoms.⁴⁰ Anders and Boston stated that in cases in which albuminuria has persisted for some time its disappearance signifies approaching danger and probably an early death.

EXPERIMENTAL

As far back as 1906, Bloodgood suggested the possibility of extracting from the medullary tumors some specific serum for therapeutic purposes and felt that it should be tried.

With the premise that multiple myeloma might be a systemic disease of infectious origin, Harbitz⁶³ injected the tumor substance into animals; the results were negative in all cases.

Furth⁶⁴ showed that myeloid leukemia of mice can be readily transmitted to healthy mice by transfer of tissue which contains lime cells. He demonstrated that in almost every mouse in which resistance had been lowered by roentgen irradiation the inoculation was successful. He produced myeloid leukemia (a diffuse disease) in mice by intravenous inoculation of large doses and multiple myeloma (tumor formation) by subcutaneous or intraperitoneal inoculation.

At our suggestion, Dr. F. Byron, of the department of pathology of the Albany Hospital, carried out the inoculation of animals with tissue removed from the patient in case 1 of our series. On April 28, 1937, within one hour after the death of the patient bone marrow from the sternum was inoculated into laboratory animals at the sites indicated in table 2. The mice and the rats were killed three months

TABLE 2.—*Data on Inoculation of Plasma Cell Myeloma*

Animals	Species	Site of Inoculation
3.....	Mice	Subcutaneous
2.....	Mice	Intraperitoneal
2.....	Rats	Subcutaneous
2.....	Rate	Intraperitoneal
1.....	Hen	Subcutaneous
1.....	Hen	Intraperitoneal

after inoculation; there was no evidence of growth of the transplanted tissues at autopsy on August 6. The hens were kept for six months before being killed. No evidence of growth of the transplanted tissues was present at autopsy on November 2.

Ravdin and Morrison⁶⁵ reported that a "marked decrease in serum calcium after thyroparathyroidectomy retarded ossification, although it did not prevent union." In 1 case of our series there was hypercalcemia, and yet at autopsy no parathyroid tissue was found, even though the dissection was painstaking and the tissue which was subsequently removed as possibly containing the parathyroid glands was examined in serial sections. Bulger, Dixon, Barr and Schregardus,⁶⁶ finding a similar occurrence in a case in their series, hypothesized that the para-

63. Cited by Oftedal.¹⁰

64. Furth, J.: *J. Exper. Med.* **61**:423-445 (March) 1936.

65. Ravdin, I. S., and Morrison, M. E.: Ossification After Fracture: Experimental Study, *Arch. Surg.* **17**:813-828 (Nov.) 1928.

66. Bulger, H. A.; Dixon, H. H.; Barr, D. P., and Schregardus, O.: *J. Clin. Investigation* **9**:143-190 (Aug.) 1930.

thyroid gland plays a role in myelomatosis and other generalized bone diseases, as there is a similarity between these diseases on the basis of the disturbance of calcium balance that is common to them.

RELATION BETWEEN HYPERPLASIA OF PARATHYROID GLANDS AND MYELOMA

The fact that hyperplasia of the parathyroid glands may occur with myeloma has been cited as evidence that the latter disease is of parathyroid origin.⁶⁷ However, hyperplasia of the parathyroid glands has been observed also with metastatic carcinoma of bone, with rickets and with osteomalacia, and the majority of observers agree that hyperplasia of the parathyroid glands is undoubtedly a secondary, rather than a primary, factor in these conditions.

There are also reliable records of cases of multiple myeloma in which the calcium and phosphorus metabolism was normal and normal parathyroid glands were found at autopsy.

DIFFERENTIAL DIAGNOSIS

In reviewing the literature one is rather surprised to note the varied conditions which have been mistaken for multiple myeloma, and yet to the already long list we must add flatfoot. A diagnosis of flatfoot was first made and followed up therapeutically in 1 of the 5 cases reported in this paper. Neuritis, lumbago, rheumatism, chronic nephritis, chloroma, tumors of the spinal cord, renal rickets, metastatic carcinoma, metastatic hypernephroma, bone cysts, Pott's disease, Paget's disease, osteomalacia, osteogenesis imperfecta, Hodgkin's disease, generalized xanthomatosis, fibrocystic disease, all osteolytic bone lesions, enchondroma, basophilic adenoma, osteogenic sarcoma, endothelioma of Ewing and hyperparathyroidism have all at times been confused with multiple myeloma.

Owing to the rarity of multiple myeloma there is a "low index of suspicion" ²⁵ among the physicians, especially when few cases seem to be alike and variations numerous. It is a disease which at times must be worked out by the pathologist, the chemist and the radiologist. The physician's part in the diagnosis is to suspect the condition and call for aid from the three aforementioned specialists. Even then a wrong interpretation of the roentgenograms, an error in diagnosis at biopsy and mistakes in chemical technic may well veil the identity of the condition for a variable length of time. One should be on guard, however, when-

67. Camp, J. D.: Roentgenologic Changes in Malacic Diseases of Bone, in Collected Papers of the Mayo Clinic and the Mayo Foundation, Philadelphia, W. B. Saunders Company, 1935, vol. 18, p. 1095.

ever an adult, especially a man, between the ages of 40 and 60, presents any or all of the following signs and symptoms:

1. Mild so-called rheumatic pain, at first perhaps generalized and impossible for the patient to locate definitely; the least contact may be dreaded; the pain is subject to acute exacerbations following a period of comfort for days, weeks, perhaps months; and yet there is no apparent invasion of the joints
2. Backache or severe thoracic pain
3. Spontaneous fracture
4. Progressing weakness and apparent anemia
5. The presence of a bony tumor mass, especially of the ribs, the sternum or the clavicle
6. Large amounts of albumin in the urine, with or without casts
7. Lumbar pain, with or without paraplegia
8. Continued low blood pressure with a nephritic syndrome
9. Shortening of stature

These clinical signs and symptoms, each and every one of them, should predicate the possibility of the existence of multiple myeloma or of one of the following conditions: (1) hyperparathyroidism, (2) metastatic carcinoma, (3) endothelioma of Ewing, (4) Paget's disease, (5) osteogenic sarcoma, (6) Hodgkin's disease, (7) lymphoblastoma (lymphosarcoma and leukemia), (8) neuroblastoma, (9) hypernephroma, (10) osteomalacia, (11) osteogenesis imperfecta, (12) osteospathyrosis, (13) chloroma and (14) osteomyelitis.

A thorough physical examination may yield entirely negative results. If this happens, the situation demands investigation by the radiologist and the chemist just as promptly as though a tumor mass had been palpated or especial sites of tenderness had been located.

The radiologist should make roentgenograms of the skull, the ribs, the clavicle and a long bone, perhaps of the whole skeletal system.

The chemist should make complete and repeated examinations of the urine with special reference to the specific gravity, the presence or absence of albumin and sugar, the calcium content and most of all Bence Jones protein. Thorough and repeated examinations of the blood should be made, with estimations of calcium, phosphorus, phosphatase, total protein (including the albumin-globulin ratio), nonprotein nitrogen, creatinine, urea and uric acid. If either on clinical or on roentgen examination one finds a tumor mass, this should be surgically investigated and a specimen removed and submitted for microscopic examination. A biopsy will usually clinch the diagnosis. Physicians are urged to make postmortem examinations of the patients, for it is at the

autopsy table and in the pathologic and chemical laboratories that studies may give the clue to the cause of this at present incurable disease.

In no case of myeloma should the inoculation of fresh tissue into rats, mice, chickens and, perhaps, dogs and cats be neglected. So far inoculations have failed, but it is worth while to carry on in this particular line of work.

No observations are absolutely dependable, and there is no characteristic symptom complex. A biopsy is, of course, of paramount importance in reaching an absolute conclusion.

As Gilmore so well expressed it,

. . . While the mistakes [in diagnosis] may not influence the course of the disease, the avoidance of them may obviate embarrassment to the practitioner, unnecessary treatment of the patient, and lead to an early, correct diagnosis. The lesions nearly always start in the vertebra and are diagnosed as Pott's disease. Multiple myeloma is seldom considered when back cases are being examined.

Hyperparathyroidism.—About hyperparathyroidism it is known that excessive parathyroid secretion causes a drain of lime salts from the body, resulting in skeletal changes, classified often as von Recklinghausen's disease or generalized osteitis fibrosa cystica. The disease usually begins between the ages of 15 and 35 years; it affects mostly women. Multiple myeloma, on the other hand, is essentially a disease of later life and affects mostly men.

The initial symptoms may be identical with those of multiple myeloma. Diffuse, so-called rheumatic pains with tenderness in the bones or the joints, progressive weakness, gradual loss of weight and early fatigue are commonly found in the early stages. As the disease progresses, spontaneous fracture may occur and indeed may be the first real sign of the condition, though a careful history will usually elicit one or more of the aforementioned symptoms as having existed before the fracture. Attacks of abdominal pain with nausea and vomiting, signs of secondary anemia and frequency of urination often bring the necessity of roentgen examination to the attention of the physician. The finding of a small tumor in the thyroid region may aid in the diagnosis, though this is so rarely detected clinically that nothing should be concluded from its absence. Nephrolithiasis may accompany this condition. A determination of the chemical composition of the blood in this disease is of paramount importance. There is a negative calcium and phosphorus balance, associated with hypercalcemia and hypophosphatemia. The phosphatase activity is marked. The similarity between myeloma and hyperparathyroidism appears occasionally to be on this basis of disturbed calcium balance, for it must be borne in mind that in many cases of multiple myeloma, the calcium level is elevated, although the phosphorus and phosphatase levels are usually normal or only slightly elevated. In cases of hyperparathyroidism, the urine and

feces contain abnormally large amounts of calcium; in cases of multiple myeloma, they do not. Bence Jones protein is practically never found in the urine in cases of hyperparathyroidism, though it is commonly detected in cases of multiple myeloma.

Roentgen findings are discussed in the section of this paper on roentgenographic differential diagnosis, page 968.

Metastatic Carcinoma.—There is frequently found the primary growth or the history of one having previously been discovered and operated on, such as carcinoma of the breast or of the prostate gland. Anemia, which is usually present, is accompanied by the clinical manifestations of anemia and progressive weakness. The roentgenologic observations are as a rule typical of the disease. Bence Jones protein is not present except in rare instances. Hyperproteinemia is rarely present. There is no inversion of the globulin ratio; usually, mild hypercalcemia and increase in the phosphorus content of the blood with an increase in the phosphatase become manifest. Ordinarily, the age is above 40. Fractures are fairly frequent, especially in the long bones.

Endothelioma of Ewing.—Endothelioma of Ewing regularly occurs in the first two decades of life, especially in men. Trauma is undoubtedly a predisposing factor; multiple skeletal involvement is rare. The shafts of the tibia and fibula are most often the sites of the disease, and the roentgenograms are characteristic. The presence of Bence Jones protein has never been reported with this disease, and the results of chemical analysis of the blood are usually negative, though there may be a slight increase in calcium and in phosphatase. Fractures occur only in rare instances. As the disease advances, secondary anemia may occur.

Paget's Disease.—Of itself Paget's disease is rarely confused with multiple myeloma, but it occasionally happens that malignant changes may so change the picture as to render intensive study necessary. Patients with this disease are over 45 years of age and mostly men. The square skull, the lateral bowing of the femurs and the tibias and the lordosis in patients with this disease readily suggest the diagnosis of this condition. The roentgen observations of marked new bone thickening, of a woolly appearance of the bones of the skull and of generalized skeletal involvement are quite pathognomonic. There is an absence of Bence Jones protein. Determinations of phosphatase show an enormous increase. The content of calcium in the urine is decreased.

Osteogenic Sarcoma.—Generalized skeletal involvement is extremely uncommon; constitutional signs are consistent with the blood picture of anemia. Fractures and the presence of Bence Jones protein are uncommon. There is an increase in the calcium and the phosphorus of the blood, and the phosphatase level is elevated. In a recent case of

ours, phosphatase was as high as 11.6 Bodansky units. The total protein may be high, though the ratio of globulin and albumin is within normal bounds. Roentgen findings are usually typical, and the lesion generally occurs primarily at the end of a long bone.

Osteomalacia.—Osteomalacia is rarely confused with multiple myeloma, and yet the multiplicity of the lesions, the frequency of fracture and the generalized osteoporosis may be mistaken for multiple myeloma. An analysis of the signs and symptoms of this disease should readily suggest the correct diagnosis. It is essentially a disease of women at the child-bearing age or at senility, though it must be remembered that it may occur in men. It is a slow and progressive osteoporosis most especially involving the thorax, the pelvis and the long bones. No Bence Jones protein is found. The blood calcium and phosphorus are decreased, while the phosphatase shows an increase, perhaps marked. Fractures are common. This disease has a well defined roentgen picture and is rarely associated with bone cysts.

Hodgkin's Disease.—Morrison⁶⁸ expressed the opinion that Hodgkin's disease is a loose diagnostic term for a number of hematogenic tumor growths. The osseous system is involved in from 10 to 50 per cent of the cases. Often there are no clinical signs, and the disease is found only by roentgenograms. In rare instances Hodgkin's disease may occur primarily in the bone.

Hodgkin's disease, lymphosarcoma, lymphoblastoma and leukemia will be discussed as a group with regard to the problem of differentiating them from myeloma. All sometimes give rise to generalized skeletal involvement, and the similarity of the signs and symptoms presented by this group of diseases is so marked that without biopsy it may be impossible to differentiate them. Although the age index is below that of myeloma, this group of diseases may affect patients up to the age of 60 or older. Vague pains in the bones and joints, abdominal discomfort, nausea and vomiting, loss of weight and strength, spontaneous fracture and even fever may be present in cases of this group of diseases as well as in cases of myeloma. The blood will show, at least in the later stages, the picture of secondary anemia, or in cases of leukemia, the typical picture of that disease. The occasional occurrence of eosinophilia with Hodgkin's disease may be a helpful aid to diagnosis. Glandular enlargement, so commonly present in cases of Hodgkin's disease, also helps. Roentgen examination is of great importance. See the section on roentgenographic differentiation, page 968. Bence Jones protein is seldom present in the urine in patients with this group of diseases; if it is, one should seriously consider the possibility of myeloma. Chemical examination of the blood may or may not be helpful. In cases

68. Morrison, M. C.: *Canad. M. A. J.* 34:393-396 (April) 1936.

of Hodgkin's disease there is more likely to be an increase in the blood calcium, though there are many cases of myeloma in which hypercalcemia is present. An increase of phosphatase and a decrease in the phosphorus content of the blood is important. Seldom, if ever, is there a decrease of phosphorus in the blood of the patient with multiple myeloma, though there is sometimes a slight increase in the phosphatase.

Neuroblastoma of the Adrenal Glands.—Neuroblastoma of the adrenal glands is essentially a disease of infancy and early childhood. The first symptom may be bone pain; occasionally an enlarged bone is the first sign. Hematuria or perhaps secondary anemia may first bring the physician's attention to the possibility of the presence of this disease. A mass in the region of the kidneys usually confirms the diagnosis. See the section on roentgenographic differentiation that follows. As the lesion is of such a destructive nature, phosphatase may be increased.

ROENTGENOGRAPHIC DIFFERENTIATION

Myeloma.—In the interpretation of roentgenograms taken in cases of suspected myeloma, it must be understood "that in order to arrive at a correct opinion the Röntgen-ray must show in detail the structure of the bones examined and the plates must be read by a person who can detect abnormal difference in density even though slight."⁴⁸

The most characteristic feature is the diminished density of the involved bones associated with absorption and replacement of lime salts by tumor tissue. The skull and the other bones usually show sharply punched-out holes. These holes may be extremely numerous. Within the tumor the absorption of bone is complete,⁶⁰ producing a rounded central area, which is sharply demarcated. In other words, no bone production is evident; there is no compensating hyperostosis. As the tumor grows, the periosteum and the epiphysis become invaded, and there gradually appears the diminished density mentioned.⁵²

The lesion is usually central and multiple, though the tumor may appear as a solitary central mass, gradually destroying and absorbing the cortex in all directions.⁶⁰

"It should be constantly borne in mind that bone resorption, which is practically always present, may be the key to the histogenesis."⁶⁹

Flax said, "So far as is known, the neoplasm does not metastasize but remains locally destructive." Our cases and those of others tend to disprove this assertion.

It must be remembered, however, that there is nothing definitely characteristic about the multiple punched-out destructive lesions; therefore, other types of destructive bone lesions must always be taken into consideration. Fracture is extremely common.

69. Graham, E. A.: Year Book of General Surgery, Chicago, The Year Book Publishers, Inc., 1932, p. 125.

Endothelioma of Ewing.—Endothelioma of Ewing is usually found in the midshaft region of a long bone, especially in that of the tibia or the fibula. There may be metastasis to any part of the skeletal system, the lungs, the lymph nodes and other soft tissues. There is involvement of a single bone early in the disease, with later dissemination to other bones. The tumor begins within the medullary canal and produces an infiltrating soft mass which erodes the cortex more or less extensively. It may break through widely and lift the periosteum, stimulating extensive formation of new bone. As a rule, the density of the bone is increased by its vigorous reaction to tumor invasion in the subperiosteal and endosteal regions. The shaft becomes expanded, and the cortex widens and becomes dense. The marrow cavity becomes mottled, and finally both cortical and medullary destruction appears. At first, the formation of bone predominates, giving rise to either parallel or radiating spicules. The tumor tissue itself possesses no properties of osteogenesis; the so-called onion cell formation is the result of multiple parallel rows of reactive bone being separated by tumor tissue. In some cases the extent of bone reaction is proportionately greater than the rapidity of tumor growth, resulting in a broad sclerotic shaft. There may be transverse striations, fine hairlike processes projecting at right angles from the periosteum. It must be remembered that this tumor has no great tendency to metastasize to any skeletal sites, but this may occur, as mentioned before.

Hyperparathyroidism.—Various stages of hyperparathyroidism present varied roentgen pictures. The most constant finding is a generalized reduction in the density of the vault of the skull, which is characterized by a fine, porous appearance with scattered areas of moderate thickening but with no dense areas of calcification; generalized skeletal involvement usually follows. Lacunar resorption with fibrosis of the bone marrow and the formation of osteoclastoma is noted roentgenographically. In about half, or a little over half, of all the cases, cysts are present too. General osteoporosis occurs, more pronounced in some areas than in others, but formation of bone does not cease. Pathologic fracture is common.

Metastatic Carcinoma.—Osteolytic metastases simulate most closely the lesions noted in cases of multiple myeloma. The former are usually less circumscribed, and large isolated lesions are common—an uncommon observation in cases of multiple myeloma. In cases of osteolytic metastasis a definite differential roentgen diagnosis may be impossible. The presence or operative history of primary carcinoma may establish the diagnosis.

Osteoplastic metastases are regularly more easily differentiated. These lesions are in close proximity to the nutrient arteries; they are

not so extensively distributed as multiple myeloma. Although the bone is infiltrated by the tumor, which produces absorption of bone, there is stimulating osteogenesis on the part of the local bone, and production of bone is present throughout the metastatic areas. The bone is thus strengthened, and although pathologic fracture occurs, it is far from common. Gross shortening of the spine, if the spine is involved, is less frequent than in cases of multiple myeloma, and unless there has been primary carcinoma of the cervix or carcinoma of the breast, the ribs are rarely involved, a condition frequently noted in cases of multiple myeloma.

Osteolytic or osteoclastic metastases have much the same distribution as plastic lesions, but they destroy bone by ossifying and stimulate little formation of surrounding new bone. The osteolytic type of metastatic carcinoma simulates multiple myeloma most closely. The former is ordinarily less circumscribed, and isolated lesions may be much larger. The presence or history of operative removal of primary carcinoma establishes the diagnosis.

Paget's Disease.—In cases of Paget's disease there is lacunar resorption, but apposition is more marked, and regional areas of dense ossification or calcification are common. The characteristic appearance of the skull is described as woolly. The bones of the calvarium are remarkably thickened and made up of areas of varying density, with an inner and outer table that is fuzzy. The tibias become bowed. Formation of cysts may occur beneath the cortex. The pelvic bones and the femurs when these are involved present similar characteristics. There is widening of bones by new bone of decreased density. Bone absorption is replaced by ossification of a low order. The bones become elongated and enlarged; added to this is the bending. Lytic changes in the medullary cavity are extremely rare, unless a malignant lesion accompanies the condition. There are smooth, expanded cortices, not the irregular margins of metastatic carcinoma.

REPORT OF CASES

CASE 1.—D. A., a 57 year old white farmer, was admitted to the Albany Hospital on March 24, 1936. His chief complaint was pain in the back, in the right side of the chest and in the shoulders.

History of Illness.—In June 1935, the patient was jacking up his automobile, when he felt a sudden catch in the left side of his chest. It was so painful that he could hardly straighten up. He applied adhesive strapping, but the pain became worse and radiated to his left shoulder and back. About ten days later he turned suddenly and felt a sharp snap in his back. It was several moments before he could straighten himself. At this time he had severe pain over his whole chest and dyspnea. He was treated by his family physician with heat, strapping, rest and colloidal sulfur. He was told that he had pleurisy.

In August 1935 roentgenograms were taken by a roentgenologist. The patient stated that he was not informed of the interpretation of the plates. He did little work after that. Whenever he exerted himself at all, he had severe, sharp pains in his chest, shoulders and back. He was seen by several physicians. He noted a gradual decrease in stature in the last few months before admission and was considerably shorter than formerly.

Past History.—Fifteen years before admission the patient fell from a tree and struck the middle of his back on a rock. After this he had pains similar to those present on admission, but less severe. In 1909, an appendectomy was performed. No other serious illness, accidents or operations had occurred.

A review of the systems showed them to be essentially normal.



Fig. 1 (case 1).—D. A., a 57 year old farmer, the patient in case 1; note the marked kyphosis.

Familial History.—His father had died of "prostate trouble" and his mother of "creeping paralysis." Otherwise the familial history was noncontributory.

Examination.—The patient was a well developed and well nourished man, 57 years old, who walked with a hesitant gait. His shoulders were stooped, and his body appeared foreshortened. There was marked kyphosis. He experienced no particular discomfort except for an occasional dull pain in the back and throughout the chest.

The head was normal. The pupils were equal and regular and reacted to light and in accommodation. The tongue was coated and protruded in the midline without tremor. The ears and nose were apparently normal. The pharynx was injected but otherwise apparently normal. Teeth were missing. The neck was normal and the glands not palpable. The pulmonary sounds were clear and resonant, and no rales were heard. Pain was elicited by pressure over the whole chest wall and was most severe in the lower part of the right side. The apex

beat was in its normal position. The heart was not enlarged; the sounds were regular, and no murmur was present. There was no adenopathy.

The blood pressure was 110 systolic and 70 diastolic. Through the abdomen the patient was obese. An old appendectomy scar was noted. There were no masses or tenderness in the abdomen, and there was apparently no inguinal glandular enlargement. The back was rigid, especially in the thoracic and lumbar region; there was fairly marked dorsal kyphosis, with pain on pressure over the lower thoracic vertebrae. Rectal examination revealed no abnormalities. The reflexes were normal.

The Wassermann test was negative.

The basal metabolic rate was 8 per cent.

The urine on the day after admission was normal. Bence-Jones protein was not found.

A complete examination of the blood (hemoglobin, red cell count, white cell count, differential count) yielded essentially negative results.

On the day after admission the blood calcium was 13 mg. per hundred cubic centimeters. Culture of the blood yielded no growth of bacteria.

A plaster of paris jacket was applied, and the patient was advised to return to the hospital within a few days for further hospitalization, biopsy of a rib and high voltage roentgen treatment.

The interpretation of roentgenograms by the hospital's roentgenologist favored the diagnosis of hyperparathyroidism. The patient left the hospital on March 28.

The patient was readmitted to the hospital on April 7. His condition was practically the same as it had been ten days previously. Since his discharge he had worn the plaster jacket and said he had received a fair amount of relief from it. He still had dull and continuous pain across the anterior wall of the chest and posteriorly between the shoulder blades; the pain became more acute when he moved about. He had no new complaints. There was no dyspnea and no cyanosis, and he did not appear acutely ill. Marked hyperalgesia was apparent on percussion over the lower part of both walls of the chest.

The blood pressure was 92 systolic and 68 diastolic.

On April 10, with the patient under anesthesia induced with nitrogen monoxide and ether, an incision approximately 8 cm. long was made in the area over the tenth rib on the right side, slightly anterior to the midaxillary line. In this area there was a definite neoplastic mass, semisolid in consistency and in places parchment-like to the touch. The rib was partially eroded, and the tumor had extended into the pleura beneath and toward the rib elbow. The tumor was composed of a soft reddish, hemorrhagic material. Approximately 5 cm. of the rib and surrounding tissue was removed. The microscopic diagnosis was plasma cell myeloma.

A phenolsulfonphthalein test on April 25 showed 25 per cent excreted during the first hour and 20 per cent during the second hour.

On April 12 a sedimentation test gave the following results:

Walton tube (normal, less than 6 minims [0.37 cc.] at the end of one hour)	16.5 minims
Volume of packed red blood cells (normal, 0.4-0.45 cc.)	0.4 cc.
Wintrobe method	0.26 mm. at the end of twenty minutes

The blood pressure readings, the blood counts, the complete results of the chemical examination of the blood and of the urine are given in tables 3, 4, 5, 6 and 7. For the roentgen findings, see page 982.

TABLE 3.—Blood Pressure Readings of the Patient in Case 1

Date *	Blood Pressure	Date	Blood Pressure
3/25/36.....	110/70	9/15/36.....	92/74
3/27/36.....	102/78	10/20/36.....	102/74
4/ 7/36.....	92/68	11/15/36.....	98/64
4/20/36.....	90/58	12/18/36.....	92/74
5/ 5/36.....	88/56	2/ 4/37.....	104/80
5/25/36.....	81/62	4/17/37.....	110/70
6/15/36.....	84/60	4/25/37.....	100/50
7/10/36.....	90/68	4/27/37.....	90/58
8/ 7/36.....	96/76		

TABLE 4.—Blood Counts of the Patient in Case 1

Date	Hemo- globin, per Cent	Red Blood Cell Count	Color Index	White Blood Cell Count	Differential Count					Comment
					Polymorpho- nuclears	Eosinophils	Basophils	Lympho- cytes	Myelocytes	
3/24/36	95	4,650,000	1+	7,100	60	1	...	34	5	Normal
4/ 8/36	90	5,310,000	0.8	9,250	74.5	4	0.5	13.5	7.5	Normal; platelets, 225,000
4/13/36	90	6,380,000	0.7	8,200	64.5	1	0.5	31	3	Normal; many basket cells
4/16/36	87	5,890,000	0.7	6,300	76	2	0.5	15	6.5	Platelets increased
4/20/36	83	4,780,000	0.8	5,600	75	2	0	17.5	5.5	
4/23/36	83	4,070,000	1	4,700	76	1	0	20	3	
5/ 8/36	73	4,240,000	0.8	4,050	61	2	0	32	5	Normal
5/25/36	87	4,840,000	0.9	3,950	60	1	...	34	5	Normal
7/10/36	84	4,720,000	...	4,570	62	1	...	33	4	Platelets increased; many basket cells
7/26/36	79	3,830,000	...	6,300	65	2	1	29	3	Slight irregularity in the size of the red blood cells
8/ 7/36	72	3,510,000	1	7,280	61	2	1	29	7	Normal
10/20/36	77	4,010,000	...	4,800	63	1	0	32	4	Normal
11/15/36	79	3,900,000	...	4,200	69	2	1	32	5	Slight irregularity in the size of the red blood cells
2/ 4/37	75	3,720,000	...	5,100	61	1	0.5	34	3.5	No abnormal cells noted
4/17/37	80	3,800,000	1+	10,000	84	0	0	12	4	Mild achromia
4/20/37	77	3,620,000	1	8,800	82	0	0	13	5	Platelets, 430,600
4/25/37	75	3,500,000	1	8,000	80	0	0	14	6	Not remarkable

TABLE 5.—Results of Chemical Analyses of the Blood of the Patient in Case 1

Date	Calcium, Mg. per 100 Cc. (Normal, 9-11)	Phosphorus, Mg. per 100 Cc. (Normal, 3.7)	Phosphatase, Units per 100 Mg. (Normal, 2.6)	Nonprotein Nitrogen, Mg. per 100 Cc. (Nor- mal, 25-30)	Creatinine, Mg. per 100 Cc. (Normal, 1-2)	Uric Acid, Mg. per 100 Cc. (Normal, 2-4)	Urea, Mg. per 100 Cc. (Normal, 12-15)	Dextrose, Mg. per 100 Cc. (Normal, 100)	Albumin, per Cent (Normal, 4.6-6.7)	Globulin, per Cent (Normal, 1.2-2.3)	Total Protein, per Cent (Normal, 6.5-8.2)	Albumin-Globulin Ratio	Carbon Dioxide Com- bining Power, per Cent	Congo Red Test, per Cent
3/25/36	13.0
3/27/36	12.4
3/28/36	13.4
4/ 8/36	14.2	3.6	Nega- tive	36.8	1.31	2.14	10.4	86.6
4/19/37	12.6	4.0	3.6	60.0	1.52	2.10	29.6	126.6	5.1	4.1	9.2	1.2
4/26/37	9.7	2.8	3.4	1.70	19.5	...	4.6	2.8	7.4	1.6
4/27/37	31.0	1.20	74.0
4/30/37	44 re- moved
4/27/37	61	...

Treatment and Course.—While in the hospital the patient received a course of high voltage roentgen therapy. He was discharged on April 27. During the summer months he was seen frequently and repeated examinations of the blood, the urine and the blood pressure were made.

On August 7 the patient returned to the hospital for another course of high voltage roentgen therapy. He said that he had experienced considerable improvement since his last admission; his chief difficulties now were pain in the right shoulder, stiffness in the back of his neck and, at times, a sense of suffocation. He also noticed increased frequency of urination.

TABLE 6.—*Results of Examinations of the Urine of the Patient in Case 1*

Date	Reaction	Specific Gravity	Albumin	Sugar	Acetone	Diastatic Acid	Bile	Microscopic Observations	Bence Jones Protein
3/25/36 (1st admission)	Neutral	1.015	0	0	0	0	0	0.....	0
4/ 7/36 (2d admission)	Acid	1.015	..	0	0	0	0	Few white blood cells.....	+
4/ 8/36	Acid	1.011	0	0	0	0	0	Few granular casts.....	0 (a.m. and p.m.)
4/ 9/36	Acid	1.012	0	0	0	0	0	Granular casts; few white blood cells	+
4/10/36	0
4/11/36	0
4/12/36	+
4/13/36	+
4/14/36	0
4/15/36	Acid	1.020	+	0	0	0	0	Rare granular cast; calcium oxalate	+
4/16/36	0
4/17/36	0
4/18/36	0	0	0	0	0	0	0
4/22/36	Acid	1.020	0	0	0	0	0	Occasional white blood cell	0
5/ 5/36	Neutral	1.012	Trace	0	0	0	0	Negative.....	0
5/ 8/36	Acid	1.010	0	0	0	0	0	Occasional granular cast..	+
5/19/36	Acid	1.022	0	0	0	0	0	Granular casts.....	+
5/25/36	Acid	1.014	0	0	0	0	0	Occasional white blood cell	0
6/15/36	Acid	1.012	0	0	0	0	0	Negative.....	+
7/10/36	Acid	1.010	0	0	0	0	0	Granular casts.....	0
7/26/36	Acid	1.014	0	0	0	0	0	Few hyaline casts	+
8/ 7/36	Alkaline	1.008	0	0	0	0	0	Negative.....	0
9/15/36	Acid	1.020	Trace	0	0	0	0	Negative.....	+
10/20/36	Acid	1.014	0	0	0	0	0	Occasional granular cast..	0
11/15/36	Acid	1.024	Trace	0	0	0	0	Negative.....	+
12/ 8/36	Acid	1.020	0	0	0	0	0	Granular casts.....	0
2/ 4/37	Acid	1.004	Trace	0	0	0	0	Negative.....	0
4/17/37	Alkaline	1.000	4+	0	0	0	0	Occasional granular cast	0
4/20/37	Acid	1.012	1+	0	0	0	0	White blood cell detritus	0
4/21/37	Acid	1.014	Trace	0	0	0	0	White blood cells.....	+
4/24/37	Acid	1.010	Trace	0	0	0	0	0
4/25/37	Acid	1.012	Trace	0	0	0	0	+
4/26/37	Acid	1.012	Trace	0	0	0	0	0
4/27/37	+

Although the patient's pain was better, it was noted that his breathing was more difficult and that the kyphosis had increased. Extension, lateral bending and rotation of the head were performed incompletely and with deliberation. Flexion was normal. The head was held slightly fixed in walking. The fourth and the fifth ribs were bilaterally prominent; the sternum was bulging, and the prominence and sagging of the dorsal vertebrae had increased. There was generalized tenderness to deep pressure over the whole thorax, and slight tenderness was noted in the upper part of the dorsal region of the spine and over the right scapular region. The lungs were clear and resonant, and there was no apparent mediastinal involvement. A soft systolic murmur had developed at the apex without axillary transmission. The pulse rate was 102. The blood pressure was 96 systolic and 76 diastolic.

The abdomen had become more prominent and somewhat firm. Tenderness to deep pressure was present under both costal margins, and there was voluntary rigidity in the epigastrium. The back was held rigid. There was moderate pitting edema of both ankles. The reflexes had become hyperactive. No neurologic signs were evident.

The patient was discharged from the hospital in August 1936. After his discharge he was frequently observed; blood counts and urinary analyses were made, and blood pressure readings were taken. The patient's condition remained about the same until April 10, 1937, when his difficulty in breathing became more pronounced; pain in the neck, in the shoulders and in both legs became more intense, and so did the pain in the left side of the neck and the jaw. Difficulty in swallowing appeared as a new symptom. He again entered the hospital on April 17.

Examination at this time showed a fairly well developed and nourished man in considerable respiratory distress. His face was cyanotic and his neck diffusely swollen. Excursions of the nasal alae were pronounced. The skin was warm and moist. The arms, the abdomen and the wall of the chest were of a bronze color. The scleras were slightly yellow. There was tenderness at various points on the scalp, as well as some irregularity, but no definite soft spots were noted. Near the hair line on the forehead there were several small firm lumps about the size of a pea. There was bilateral edema of the neck with a feeling of induration. There were scattered nodes, the size of large lima beans, tender, fixed and irregular, particularly in the submaxillary region. The chest appeared symmetric, but there was marked tenderness of the whole thoracic wall to palpation. The breast bone was protuberant. The breath sounds appeared normal, and no rales were heard. Heart sounds were apparently normal. The abdomen was distended and firm, no tenderness was elicited, with the exception of a small tender area at the right costal margin, and no masses were felt. The liver, the kidneys and the spleen were not apparently enlarged. The reflexes were hyperactive. The Babinski sign was equivocal on both sides. Cyanosis of the extremities was noted. Along the long bones there was considerable tenderness to pressure. On the day after admission the patient's condition was unchanged except that there appeared an increase of difficulty in breathing. The Wassermann test was negative.

On April 19 the dyspnea became more pronounced; the pulse was weak and irregular, and difficulty in swallowing added to the patient's discomfort. In the days following, pain in the head and the neck with no typical distribution, cyanosis, dyspnea, delirium, dysphagia, sudden rises in temperature and increased bronzing of the skin preceded death, which occurred on April 28.

Autopsy (Dr. G. H. Klinck Jr.).—The body was that of a white man 58 years of age, 63 inches (157.5 cm.) in length, well developed and well nourished. It was warm and free from rigidity. The skin had a slight yellowish tinge. There was slight edema of the lower part of the legs, and the hands appeared somewhat puffy. The hair was gray and plentiful. The eyes were light brown with pupils equal, regular and measuring 0.8 cm. in diameter. There was a moderate arcus senilis on each side. The conjunctivas were pale in general, but the inner surfaces of the lower lids showed a few minute red points suggestive of petechiae. The subcutaneous lymph nodes were not remarkable. The neck was thick and short. The submaxillary glands were not enlarged. The nasal passages and the mucous membranes of the mouth were not remarkable. The teeth were all absent and were replaced by plates. The hair over the chest and the abdomen was profuse.

There was a healed oblique surgical incision 5 cm. in length in the right lower quadrant of the abdomen. There was a healed surgical incision 8 cm. in length over the right tenth rib in the posterior axillary line. The body was opened by the usual autopsy incision. The subcutaneous fat was normally plentiful, and the muscles were of a good color. There was no subcutaneous edema.

The peritoneal cavity was free from fluid and adhesions. The diaphragm reached the level of the fifth rib on the left and the fourth on the right. The mesenteric lymph nodes could not be identified. The retroperitoneal lymph nodes were few in number and difficult to identify. The nodes found were small.

The right pleural cavity contained about 60 cc. of clear yellow fluid; the left pleural cavity, 450 cc. There were no adhesions on either side. The lungs almost completely filled their respective cavities.

The mediastinum showed nothing unusual.

The pericardial cavity contained about 30 cc. of clear yellow fluid, and its linings were smooth, pale and glistening.

The heart weighed 400 Gm. A normal amount of subepicardial fat was present. The coronary arteries were not tortuous and showed only a mild degree of sclerosis, not out of proportion to the age of the patient. The myocardium was of normal consistency, and the muscle generally was of a good red color. The lateral wall of the left ventricle was the site of numerous rather long and narrow fibrous scars which gave the muscle in this situation a fairly firm consistency. The endocardium and the valve leaflets were not remarkable. The wall of the left auricle was somewhat thicker and firmer than normal. The endocardium of the left auricle was unusually pale and appeared thickened.

The aorta presented a moderate degree of atherosclerosis, which was most marked in the abdominal portion.

The right lung weighed 450 Gm. and the left 315 Gm. Except in weight, they were almost identical. The pleural surfaces were smooth and glistening and showed the usual amount of anthracotic pigmentation. The posterior portions of both the upper and the lower lobes were collapsed, wrinkled and soft. The remaining portions of the lung tissue were gray, fluffy and air bearing. Multiple sections failed to reveal pathologic changes other than atelectasis of the posterior portions of both the upper and the lower lobes of the lungs. There was no evidence of inflammatory reaction.

The mucous membrane of the trachea was unusually pale; it was free from any evidence of inflammatory reaction. The trachea was opened anteriorly and the incision extended through the larynx. The laryngeal mucous membrane was pale. There was nothing unusual in the vocal cords. It was not possible, however, to rule out edema of the soft tissues above the vocal cords, which might have accounted for the respiratory difficulties experienced during life. The main branches of the bronchial tree were opened; the mucous membrane was pale and free from inflammation.

The thyroid gland presented nothing unusual. It was reflected on each side and a careful search made for the parathyroid glands.

Two minute masses of tissue which might have represented the parathyroid glands were found on the right side. No masses suggestive of parathyroid tissue were present on the left.

The spleen weighed 70 Gm. It was small, soft and flabby. The capsule was smooth and bluish purple. When sectioned, the parenchyma had a finely granular, reddish appearance, which did not indicate any pathologic change.

The esophagus and the stomach were not unusual. The small intestine in places showed congestion of the mucosa. Nothing else was noted. The large intestine was not remarkable. The appendix could not be identified.

The pancreas was large and firm. When it was sectioned, nothing unusual was observed.

The liver weighed 1,250 Gm. It appeared somewhat small in comparison with the size of the patient. The surface was smooth, and the organ was of normal consistency. Sections revealed slight accentuation of the hepatic markings. There was no evidence of increased translucence of the tissues which would suggest amyloid infiltration.

The gallbladder was of normal size and was thin walled; it was free from stones and contained thin yellowish green bile. All the ducts were patent.

The adrenal glands were of normal size but were somewhat softer than usual. The cortical tissues were bright yellow. The medullary tissues were clearly defined and appeared creamy white and firm.

Each kidney weighed 140 Gm. Both kidneys were surrounded by extremely pronounced perirenal capsules of fat and fibrous tissue. The renal capsules proper stripped away when the perirenal capsule was removed. The kidney surfaces presented to a slight degree a finely granular appearance and were reddish purple, as though congested. On section the normal renal markings were present. The cortical and medullary tissues were congested. There was no evidence of amyloidosis. The pelvis were not remarkable. The renal arteries and their larger branches appeared free from sclerosis.

The bladder contained about 200 cc. of clear yellow fluid. The bladder wall was of normal thickness. The mucosa was pale.

The prostate gland was of normal size, and when sectioned, presented no abnormalities. The seminal vesicles were not remarkable. Grossly, the testes were normal in appearance.

The head was of normal shape and covered with a thick, heavy growth of hair. The scalp was incised in the usual manner and reflected.

The appearance of the calvarium and the bones of the skull will be described later. The calvarium was removed with some difficulty because of marked adherence to the dura.

After the calvarium was removed it was observed that almost all the inner table on the left side was adherent to the dura. This inner table appeared as a coral-like formation of spicules. The leptomeninges were not remarkable.

The brain weighed 1,330 Gm. It was of normal consistency, and the meningeal vessels contained the usual amount of blood. A mild degree of thickening of the vessels at the base was noted.

The pituitary gland was removed as soon as the brain was exposed and placed in Regaud's fixative solution exactly five hours after death. Grossly, the gland was not remarkable.

When the scalp was reflected, the calvarium presented a most unusual appearance. Innumerable, sharply circumscribed, generally circular, bright red foci, averaging 3 mm. in diameter, were present. A few larger uncircumscribed foci of redness were noted. The calvarium was unusually thin and cut with extreme ease. The edges were unavoidably broken when the calvarium was pried from the base of the skull. Some force was necessarily applied in removing the calvarium because it adhered to the underlying dura. During these manipulations the inner table of the calvarium on the left was torn away and remained attached to the dura.

When the inner surface of this bone was examined, it was observed that it presented numerous large red splotches of irregular shape and size. These were clearly seen on the right side, where the inner table remained intact. On the left side, however, the inner surface of the calvarium presented a soft, gelatinous, reddish yellow tissue as a result of detachment of the inner table. This soft tissue

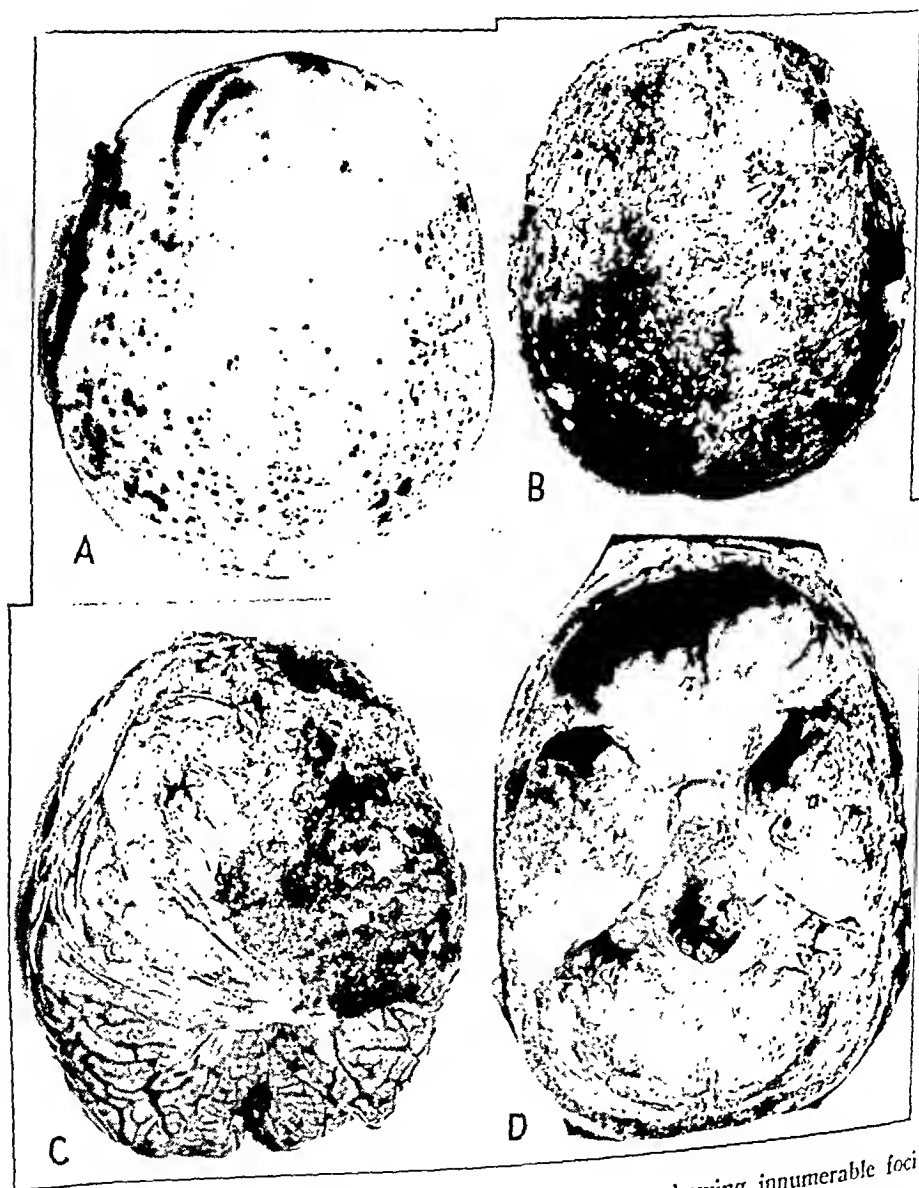


Fig. 2 (case 1).—*A*, outer aspect of the calvarium, showing innumerable foci of myeloma; *B*, inner aspect of the calvarium, showing the moth-eaten appearance of the inner table of the skull; *C*, the brain covered by the dura, showing adherence of the inner table of the calvarium on the right side; *D*, the base of the skull, showing the moth-eaten appearance of the bone due to multiple myeloma.

was characteristic of the marrow found in other bones of the body and was believed to represent the tissue of myeloma.

After the brain was removed and the dura stripped from the base of the skull, it was noted that all the bones of the base presented the same splotchy red appearance as was found on the inner surface of the calvarium. Thus it was evident that all of the bones of the skull were involved in a similar process.

Before the autopsy, the skin overlying the left clavicle was cleaned with alcohol and iodine, and the clavicle was removed under sterile conditions. A portion of this clavicle was used for animal inoculation. The cortex of the clavicle was extremely thin and, in places, even paper-like. It cut with practically no resistance. The cavity of the bone was filled with soft, mottled red and yellow tissue similar to that found in the skull. This tissue was soft, friable, translucent and, in places, almost jelly-like. It contained few spicules of bone. It was evident that the process had caused extensive absorption of bone.

The sternum was soft, and a scalpel was easily plunged through it. The marrow cavity was large and contained a dark red material similar to that found in the clavicle but of a different consistency. Marked absorption of bone had taken place, since only a few, but rather large, spicules of cancellous bone were noted. The cortex was greatly thinned out.

All the ribs were extremely thin and pliable and fractured when slight pressure was exerted on them. There was a slight deformity of the right tenth rib in the right posterior axillary line; at this site a portion of the rib had been removed in biopsy some time before.

The vertebral bodies cut with extreme ease. The intervertebral disks were not remarkable, but the cancellous spaces of the bodies presented a dark red appearance. A few rather large spicules of cancellous bone were left, but extensive absorption of bone had taken place. The tissue beneath the spicules of bone was soft, friable and intensely red. No other bones were examined.

The provisional anatomic diagnoses were: multiple myeloma; slight bilateral atelectasis; bilateral hydrothorax, and sclerosis of the left ventricular myocardium.

Examination of the Brain After Hardening in Formaldehyde Solution (Dr. G. H. Klinck Jr.).—Except for the changes resulting from fixation in solution of formaldehyde, there were no changes in the brain other than those noted when the brain was fresh. The brain was further examined by making numerous parallel frontal sections. These sections showed that the white and the gray matter of the brain were normally disposed. There was no enlargement of the ventricular system. The ependyma was smooth throughout. The choroid plexuses were without change. Multiple sections through the midbrain, the cerebellar hemispheres and the medulla revealed nothing of note.

Microscopic Examination (Dr. G. H. Klinck Jr.).—Heart: The larger branches of the coronary arteries in the subepicardial fat revealed moderately advanced atherosclerosis. No calcification was noted in sections of the vessel studied.

The myocardial fibers were of normal size and in general seemed well preserved. The branches of the coronary arteries deep within the myocardium showed numerous foci of hyaline degeneration in their walls. Other hyaline changes occurring in the connective tissues of the heart will be described later. A slightly increased amount of fibrous connective tissue surrounded the intramuscular coronary branches. In some places this fibrous tissue had extended out to replace a few of the muscle cells. Aside from these and a few other foci of fibrous tissue replacement, the myocardium showed nothing unusual.

Extremely well marked foci of hyaline degeneration were found in almost all the connective tissues of the heart. This change was characterized by the presence of large and small, irregularly shaped, branching masses of dense, clear, some-

what acidophilic, structureless substance. This change was apparent in the sub-epicardial connective tissue as well as in the subendocardial connective tissue and in the connective tissue throughout the heart. It was most marked in the subendocardial tissues. This hyaline change, while not uncommon in connective tissue, was extremely marked in this case. A similar hyaline degeneration could be observed in almost all the branches of the coronary arteries within the myocardium as well as in the subendocardial and the subepicardial connective tissue. In some cases it appeared as though muscle fibers of the heart were being replaced by this hyaline substance, but careful examination revealed that the changes were occurring solely in connective tissue. Examination of a section of the wall of the left auricle revealed that the endocardium was loose in structure and much thickened.

Aorta: The sections studied revealed little of note. The submesothelial connective tissue of the adventitia was infiltrated by moderate numbers of small round cells which appeared to be lymphocytes. The vessels of the adventitia had unusually thick walls but were free from perivascular infiltration. In some of the vessels there was a suggestion of hyaline change.

Trachea: A section of the upper portion of the trachea showed marked edema of the connective tissue outside of and within the cartilaginous rings. The edema was most marked in the latter site. The connective tissue of the trachea showed slight hyaline degeneration. A large portion of the epithelial lining of the trachea was absent, but this was interpreted as a result of postmortem change or artefact. Nevertheless, well marked subacute tracheitis was present. The subepithelial connective tissue, in addition to edema, revealed the presence of numerous lymphocytes and a moderate number of polymorphonuclear leukocytes, the majority of which were eosinophils. The changes just described possibly account for the respiratory distress experienced by the patient shortly before death.

Lungs: In all sections of lung studied there was slight thickening of the connective tissue of the pleura, and in places hyaline degeneration was noted. Mild acute bronchitis and bronchiolitis were present. The branches of the bronchial tree contained varying numbers of polymorphonuclear leukocytes, and in some instances the walls of the tubes were mildly inflamed. Some sections of lung showed partial collapse of the alveoli. In these situations the remaining air spaces contained small numbers of polymorphonuclear leukocytes. In other sections of lung the pulmonary tissues themselves were mildly inflamed. These changes were interpreted as representing pneumonitis rather than real pneumonia. There was no evidence of myeloma in any of the sections studied. A few alveoli contained large numbers of polymorphonuclear leukocytes, fibrin and a few erythrocytes. The lungs in general showed mild pneumonitis, but in a few places there was early bronchopneumonia.

Diaphragm: Sections of the diaphragm revealed no changes worthy of note. No infiltration of plasma cells was noted.

Spleen: The capsule of the spleen was not remarkable. The splenic sinusoids contained normal numbers of erythrocytes. The splenic pulp was cellular, but no abnormal cells were noted. The usual degree of thickening of the arterioles of the spleen was observed.

Gastrointestinal Tract: Sections of the stomach, the small and the large intestine revealed no abnormalities.

Pancreas: Histologically, the pancreas presented nothing unusual. The islet tissue was plentiful and was normal in appearance. The acinar cells were well preserved.

Liver: The tissues of the liver presented nothing worthy of note histologically. The parenchymatous cells were unusually well preserved. The sinusoids contained the usual number of erythrocytes. The portal canals and associated structures were not remarkable. No infiltration of plasma cells was present in the sections studied.

Adrenal Gland: A section of one adrenal gland revealed that the cells were unusually well preserved. The gland was divided into the usual zones. The adjacent fatty and fibrous tissues showed numerous foci of hyaline degeneration. This change was also noted in some of the blood vessels in the vicinity.

Kidneys: In the kidneys a few small subcapsular scars were observed. These consisted of dense fibrous tissue infiltrated by varying numbers of lymphocytes. The renal tissues in general showed little worthy of note. The glomeruli were unusually well preserved. The vascular systems of the kidneys were unchanged. The renal pelvises were not unusual.

Bladder: The vesical mucosa was thin but intact throughout. No evidence of inflammatory reaction was noted.

Prostate Gland: A mild degree of benign glandular hyperplasia was present. A few of the acini contained small numbers of polymorphonuclear leukocytes, and the walls of these acini were mildly inflamed. The section included a portion of a seminal vesicle, but this was not remarkable.

Testicle: A section of one testicle revealed slight edema of the interstitial tissues. The majority of the tubules were well preserved, but some of them were sclerosed. Spermatogenesis had been taking place.

Peribronchial Lymph Nodes: Sections of two peribronchial lymph nodes revealed rather large deposits of anthracotic pigment. The tissues of the gland were moderately sclerosed, and the lymph sinuses were in some instances considerably dilated. A normal number of plasma cells was scattered through the glands, but the presence of these cells was not interpreted as infiltration by myeloma.

Parathyroid Gland: Sections taken from blocks of tissue were thought possibly to contain parathyroid tissue and were examined. These blocks showed only connective tissue and thyroid gland substance. There was no evidence of parathyroid tissue in any of the sections studied.

Thyroid Gland: Sections of the thyroid gland revealed the acini to be large and the lining epithelium to be flat. A few foci of chronic inflammation were present. These changes were interpreted as representing early colloid goiter.

Voluntary Muscle: A section of voluntary muscle revealed no unusual changes.

Bone Marrow: The marrow of the clavicle, the ribs, the vertebra, the sternum and the calvarium was studied. In all instances the same changes were noted. Considerable absorption of bone had taken place, and in some places this was extremely marked. It was noted, however, that the changes which were primary in the bone marrow did not extend into the adjacent soft tissues.

The site of hemopoietic tissue was occupied by large masses and anastomosing cells, which were generally of one type. The amount of fat tissue was markedly reduced by overgrowth of these cells. The type cell was rather uniform in size and, roughly, about twice the size of an erythrocyte. The cells were rarely round. Most frequently they were oval with a tendency to a rectangular shape. The rectangular-appearing cells were most numerous where the cells were assembled in dense masses. The cytoplasm of these cells was rather homogeneous, slightly eosinophilic and somewhat variable in amount. The nucleus was almost invariably located in an eccentric position. In the large majority of cells it

showed a peripheral arrangement of coarse clumps of chromatin. These cells were typical plasma cells.

Although the hemopoietic tissues were largely replaced by these plasma cells, there was evidence of remaining hemopoietic tissue. Here and there myelocytes and metamyelocytes as well as rare mature polymorphonuclear leukocytes were seen. The amount of this tissue, however, was markedly reduced compared with the normal. Furthermore, there was evidence of erythropoiesis. In some places, where plasma cell infiltration was less marked, well formed normoblasts were present. Thus, in spite of the fact that the marrow was largely replaced by plasma cells, there was evidence of functioning bone marrow.



Fig. 3 (case 1).—Roentgenogram of the skull, showing extensive localized areas of destruction.

Dura Mater: A section of the dura showed the inner table of the calvarium firmly adhering to it. The marrow of the calvarium was firmly adherent also, and this showed changes similar to those described before.

Brain: The brain substance proper was not unusual. The subarachnoid vessels, especially those about the base of the brain, had slightly thickened walls. A section of the basilar artery revealed moderate thickening of its walls. The ependyma and the choroid plexus were normal.

Spinal Cord: Sections of the upper cervical portion of the spinal cord revealed no remarkable changes.

Anatomic Diagnoses.—The clinical diagnoses had been: multiple myeloma with metastasis to the mediastinum and to bones; questionable amyloidosis of the kidneys (because of the congo red test); chronic nephritis; chronic passive congestion of the liver; secondary anemia; Bence Jones proteinuria.

The final anatomic diagnoses as approved by Dr. Arthur W. Wright were: multiple myeloma; subacute tracheitis; edema of the trachea; acute bronchitis; mild terminal pneumonia; slight bilateral atelectasis; bilateral hydrothorax; mild sclerosis of the left ventricular myocardium; hyaline degeneration of the connective tissues of the heart, the aorta and the diaphragm; generalized hyaline degeneration of the arteries and the arterioles.

Report of Roentgen Observations.—March 24, 1936: The bodies of the sixth, the eighth and the twelfth dorsal vertebrae and that of the third lumbar ver-



Fig. 4 (case 1).—Dorsal view of the left side, showing extensive localized destruction in the clavicle, the spine of the scapula, the humerus and the ribs.

tebra showed evidence of partial collapse. There were marked atrophic changes in all the vertebral bodies and in the ribs. There was some enlargement of the distal end of the tenth rib on the right side of the chest.

These observations were consistent with hyperparathyroidism. There was no evidence of metastatic tumor in the pelvic bones or the hips. The pelvis showed uniform changes throughout.

April 8: There were many disseminated areas of decalcification scattered throughout the skull and in the body and the ramus of each mandible. These changes were consistent with hyperparathyroidism, although it was impossible to exclude metastatic new growth entirely.

There were no remarkable changes in the lower third of either the radius or the ulna or in the bones and the joints of the wrists and the hands.

April 10: Under fluoroscopic control, the area of cystlike expansion in the eleventh rib was localized by means of two hypodermic needles, one placed on the upper border of the rib at the anterior portion of the expansion and the other under the lower portion of the rib at the posterior portion of the expanded area on the right side of the chest.

May 25: There were multiple disseminated areas of decalcification throughout the skull; these suggested metastatic tumor. A comparison with the films of April 8 revealed no definite change. The thorax was foreshortened because of multiple collapse of the dorsal vertebrae. The mediastinum was not unusual in width. The trachea did not appear to be displaced. There was evidence of multiple metastatic nodules in both clavicles and in the ribs.

September 8: There were extensive localized areas of destruction throughout the skull, through the right clavicle and the right humerus and in the ribs on both sides of the chest. There was multiple collapse of the dorsal vertebrae. There were marked atrophic changes in the lumbar part of the spine and the pelvis, but there was no definite evidence of involvement by tumor. In the shaft of the right femur there were no abnormalities.

April 19, 1937: There were extensive localized areas of destruction throughout the skull, in both clavicles and through the spine of the scapulas, in each humerus, through both radii and ulnas and in the ribs, suggesting a metastatic tumor. There was evidence of multiple collapse of the dorsal vertebrae.

There was evidence of multiple areas of destruction in each femur. The tibiae and the fibulas and the bones of the feet were not remarkable. The bones of the hands showed generalized atrophic changes, but there was no definite evidence of tumor.

A comparison with the roentgenograms taken Sept. 8, 1936, revealed a definite increase in the amount of destruction.

CASE 2.—R. H., a railroad brakeman 44 years old, entered the Albany Hospital complaining of pain in the left groin "running down" to the knee.

History of Illness.—Eight weeks before admission he noted a sharp pain in the left groin which caused him to limp, and though it did not bother him a great deal, it interfered with his work. It was intermittent and was not increased by walking or exercise. Lately the pain had been more constant and more severe. For three weeks before admission it had radiated to his back, to the upper part of his left leg, to his left knee and to the upper portion of the lower part of the leg. The pain came without warning and was severe enough to keep him awake at night. He stated that concomitant with the sharp pain in his left groin eight weeks before admission, he had noted a small "lump" in the groin. This was about the size of an almond, and it had increased somewhat in size since then. He believed that the pain emanated from this lump, otherwise the latter gave him no trouble.

For eight years he had been receiving treatments for albuminuria, which was discovered by a routine railroad examination. He apparently had no symptoms relating to the urinary tract except a slight burning at the end of the penis on urination.

Past History.—Except pleurisy when he was 12 years of age, he had had no other serious illnesses, accidents or operations.

A review of the systems showed them to be essentially normal, except for albuminuria.

Familial History.—The father died of "stomach trouble"; the mother died from "stroke." Two of his brothers were dead; one from "kidney trouble" and the other from diabetes.

Examination.—The patient was a well developed and well nourished, stout man, 44 years of age, who walked with a slight limp. The skin and the mucous membranes were pale and the eyelids slightly puffy. The pupils were equal and regular and reacted to light and in accommodation. The ears, the nose, the mouth and the teeth were essentially normal. A few small and freely movable cervical glands were noted. The thorax, including the heart and the lungs, was apparently normal. The abdomen was obese; no masses were detected in it, and no tenderness or spasticity was noted. The liver and the spleen were not enlarged. In the left groin there was a hard immobile regular mass the size of an English walnut, firmly attached to the underlying tissues, painless and located in the lowest portion of the inguinal canal. Apparently, it was attached to the pelvis. There was no impulse on coughing or weakness of the abdominal rings. There was weakness of the left leg with pain on motion in the suprapubic and lower inguinal regions. There was pain in the left buttock and in the left knee on motion. No definite involvement of the left sciatic nerve was noted.

The neurologic examination gave essentially negative results. The reflexes were negative; there was no Romberg sign or clonus. Measurements of both legs were equal.

Rectal examination revealed a slightly enlarged, smooth and rather hard prostate gland. The left lobe was slightly larger than the right, and an attached mass the size of a sickle pear, immobile and painless on palpation was noted; it was apparently attached to the left pubic bone. There were no enlarged inguinal glands. (The tumor just described was apparently not a lymph gland.)

Cystoscopic examination showed no evidence of tumor formation, though along the left margin of the vesical neck there was edema with several large tortuous veins on the lateral wall. The left lateral wall showed moderate extravescical pressure, and the urethral ridge was elevated. The urethra was not depressed, and cystoscopic examination revealed less deformity of the bladder than would be suspected from the cystogram.

No growth of bacteria was obtained from the blood culture.

From the cavity of the right fifth rib *Bacillus coli* was isolated. From the abscess of the pubic bone a gram-negative bacillus which does not belong to the known group of pathogens was isolated.

The results of the examination of the blood and the urine are given in table 7. The roentgenologist's report is given on page 991.

A tentative diagnosis of malignant tumor of the pelvic bone, probably sarcoma, was made.

Treatment and Course.—The patient was discharged from the hospital fourteen days after admission.

In the meantime high voltage roentgen therapy had been instituted.

Three months later, the patient was advised to return to the hospital. At this time there was excruciating and almost continuous pain in the arms and the legs. During his stay of five days in the hospital, further roentgenograms were taken of the pelvic bones, the right femur, the skull and the ribs. The urine was again examined for Bence Jones protein (table 7). No loss of weight had been noted, and a general physical examination showed the patient's condition to be

about the same as on first admission. The mass in the groin had not apparently enlarged, and again the tentative diagnosis of malignant tumor of the pelvic bone with metastasis to the skull and the ribs was recorded.

Three weeks later the patient reentered the hospital because of the severity of the pain in the ribs, the sternum, the shoulders and the back and because of the presence of a "tumor of the head." This was an egg-sized mass located in the right frontoparietal region of the skull; it was of bony hardness with scattered areas of fluctuation and was painless to pressure. The overlying skin appeared to be uninvolved. Tenderness was elicited over the left mastoid and occipital regions, over both shoulders, the upper dorsal portion of the spine, the sternum, the lower left ribs, the right costal margin, the left pubic bone and both femurs. Over the superior ramus of the left pubic bone was a fixed, firm, tender mass about the size of a lemon.

Biopsy of the growth in the skull was performed on the day after admission. Dr. Arthur W. Wright reported the biopsy as follows: "This is a fairly rapidly growing malignant tumor, which diffusely infiltrates the scalp. The neoplastic cells are poorly differentiated but appear epithelial. They do not form any recognizable structure. The tumor is believed to be metastatic, but the source of the primary neoplasm cannot be determined."

The course of high voltage roentgen therapy was continued, but in spite of all treatment the patient died one month after his last admission.

Autopsy (Drs. J. W. Conrad and E. F. Joslin).—The body was that of a white man, well developed and apparently well nourished. He was said to be 44 years of age and appeared to be approximately that age. The body measured 66 inches (165 cm.) in length. There was no edema, but there was slight dependent lividity. The hair was gray and sparse. Through the scalp in the right frontoparietal region, about 10 cm. lateral to the midline, was an incision in the sagittal plane. It measured 2 cm. in length and was covered with a brownish black crust. The eyes were gray. The pupils were equal and round and measured 0.7 cm. in diameter. The nose and the ears were normal. The teeth anteriorly were in good condition, but the mouth could not be opened far enough to ascertain their condition posteriorly. The skin was of normal texture. There was a depressed irregular oval scar, measuring 2 by 3 cm. on the middle of the lateral aspect of the left arm. On the middle of the medial aspect of the right forearm there was a tattoo in red and blue colors of two clasped hands holding a sheaf of palm leaves (?); this measured about 4 by 7 cm. in its greatest diameters.

The body was opened by the usual midline incision from the sternal notch to the symphysis pubis. There was adipose subcutaneous tissue measuring 1 cm. over the chest and 2.5 cm. over the abdomen. The muscles were of the normal dark red color.

The diaphragm reached the level of the fourth rib on the right and the fourth interspace on the left. There was no free fluid, and on gross examination the peritoneum appeared normal. There were no palpable adhesions.

The right pleural cavity was free from fluid. There were no adhesions. Grossly, the pleura presented a normal appearance. The left pleural cavity also was free from fluid. There were a few strands of fibrous tissue between the parietal and the visceral pleura in the region of the apex of the upper lobe of the left lung. These broke with ease. Elsewhere the pleura was smooth and glistening.

The structures of the mediastinum appeared grossly normal on first examination, but subsequent dissection showed that there was a firm nodular mass of tissue in the arch of the aorta, which cut with some difficulty, the knife blade grating on calcareous granules. The cut surfaces presented a rather firm, everted whitish yellow tissue interspersed with soft caseous bluish green material.

The pericardial cavity contained about 25 cc. of clear straw-colored fluid. There were no adhesions. The linings were smooth and glistening.

The heart weighed 370 Gm. The size was compatible with the size and age of the subject. There was an increased amount of subepicardial fat, especially over the right ventricle. The heart felt somewhat softer than normal and cut with decreased resistance. The myocardium was pale. That of the right ventricle measured 0.8 cm. and that of the left ventricle 1.8 cm. in thickness. The endocardium and the valve leaflets appeared normal. The circumferential measurements of the heart valves were tricuspid, 10.5 cm.; pulmonic, 7 cm.; mitral, 10 cm., and aortic, 7 cm.

In the aorta there were no ulcerations or foci of calcification. There was a suggestive slight wrinkling of the intima in the lower abdominal portion, but it was hardly definite enough to be termed sclerosis.

The left lung weighed 430 Gm. The pleural surfaces were smooth and glistening, except in the apical region, where there were the adhesions already mentioned. Beneath the pleural surfaces were the blackish mottlings of anthracosis. The upper lobe of this lung felt as if it was of normal consistency throughout; the lower lobe posteriorly was dark purple and firm, and on section the vesicular tissue had a purplish black color and was meaty in consistency. There was a small firm whitish nodule, about 0.75 cm. in diameter, in the tissue of the lateral costophrenic tongue of the lower lobe. This sectioned with ease, and the cut surfaces presented a homogeneous everted firm whitish tissue. The bronchial tree was opened but presented nothing of note.

The right lung weighed 490 Gm. and was similar to its fellow except that there were no adhesions and no nodule was palpable in the parenchyma.

The spleen weighed 220 Gm. The capsule was of normal color and thickness but was somewhat wrinkled. The spleen was soft to touch and cut with decreased resistance. The cut surfaces presented a dark red appearance.

The esophagus was of normal size and shape. The muscular wall and the mucosa were essentially normal. The stomach presented nothing of note on the serosal surface. The mucosa was diffusely reddened and velvety. There were no ulcerations or nodules. The stomach contained a few cubic centimeters of light brownish yellow fluid.

The small and the large intestine presented a normal appearance. The appendix was 5 cm. in length, less than 0.25 cm. in diameter and of a whitish color and firm consistency.

The pancreas appeared normal.

The liver weighed 2,100 Gm. Its edges were less sharp than normal. The capsule was thin and glistening. The liver appeared somewhat pale. It sectioned with ease, and the cut surfaces presented yellowish brown parenchyma in which the markings were distinct. There were no nodules and no increase in fibrous tissue.

The gallbladder was of normal size. It was greenish black and contained no calculi, but about 5 cc. of greenish black thick bile was present. The mucosa showed postmortem erosion. The bile ducts were patent.

The adrenal glands were buried in dense adipose tissue but presented normal characteristics grossly.

The right kidney weighed 155 and the left 170 Gm. The kidneys appeared slightly small. The capsules were of normal thickness and stripped with ease, displaying fine granular cortical surfaces. There were approximately ten cortical cysts, averaging 0.8 cm. in diameter and containing whitish serous fluid within thin walls. The kidneys sectioned with normal resistance. The cortical surfaces were pale and displayed marked pinpoint reddening of the glomeruli. Grossly, the medullas presented nothing of note. There was an increase of pelvic fat.

The bladder contained about 100 cc. of cloudy yellow urine. The bladder wall was somewhat thick. The mucosa was normal.

The median lobe of the prostate gland was enlarged and bulged somewhat into the bladder. The limits of the gland could not be defined because the capsule

TABLE 7.—D.

Data	Wassermann Tests				Blood Pressure, Mm. of Mercury	Blood Counts								
	Blood					Hemoglobin, per Cent	Red Blood Cells	Color Index	White Blood Cells	Differential Count				
	Cholesterolized Antigen	Acetone Insol- uble Antigen	Precipitin (Kahn)	Spinal Fluid						Polymorpho- nuclears	Eosinophils	Basophils	Lymphocytes	Myelocytes
3/ 2/36	120/80	97	4,950,000	1.0	9,200	68	0	0	28	4
3/ 4/36	103	5,350,000	0.9	10,800	75	2	..	18	..
3/ 6/36
3/ 9/36
				with all quantities										
3/11/36
5/ 6/36
6/ 4/36	130/84	13	..
6/15/36	75	4,150,000	..	15,220	82	1
6/16/36
7/14/36
7/29/36
8/ 5/36
8/11/36

had been destroyed by a firm dense whitish yellow friable tumor, which spread laterally and anteriorly to involve the pubic bones. When the gland was sectioned, several small pockets of thick yellow purulent material were encountered; some of this material was taken for culture. The inner aspects of the pubic bones were necrotic, and spicules of bone were palpable within the neoplastic tissue. The rectum was not involved by the growth.

Grossly, the genitalia presented normal characteristics. The vertebral bodies of the thoracic portion of the spine presented slight nodular projections from their anterior surfaces. When sectioned, the vertebral bodies cut with ease, and the incised surfaces exhibited the same type of firm whitish yellow friable homogeneous neoplastic tissue already found about the prostate gland. All the ribs were studded with firm nodules of the same tissue. The ribs broke on slight pressure. In several instances the centers of the tumor nodules were necrotic and fluid in consistency.

The provisional anatomic diagnoses were: primary carcinoma of the prostate gland; metastatic carcinoma of the skull, the ribs, the left lung, the vertebrae and the pelvis; chronic vascular nephritis; atelectasis of the lungs; acute gastritis; anthracosis; cortical cysts of the kidneys.

Microscopic Examination.—Heart: The epicardium contained a large amount of adipose tissue, which extended along the connective tissue trabeculae into the myocardium for a short distance. In one section, a large coronary artery was partially occluded by irregular large fibrosed atheromas. There was slight separation of the muscle fibers of the left ventricle by fluid. The smaller blood vessels of the myocardium were congested throughout. No tumor nodules were seen. The endocardium was not remarkable.

Urine in Case 2

Specific Gravity	Urine							Bacteriologic Examination						Phenolsulfonputhalein Test	
	Albumin	Sugar	Acid	Diastatic Acid	Blood	Hyaline Casts	Bence Jones Protein	Bladder		Left Kidney		Right Kidney		Specimen 1 (Volume, 110 Cc.)	Specimen 2 (Volume, 70 Cc.)
								Smear	Culture	Smear	Culture	Smear	Culture		
1.013	0	0	0	0	Occasional red and white cells	0	0	0	0	18% excreted	17% excreted
.....	0	0
.....	0	Staphylococcus albus
.....
1.017	0	0	0	0	0
1.021	0	0	0	0	0
1.012	2+	0	0	0	0
.....	Finely granular casts	0
1.013	2+	0	0	0	Occasional red and white cells	Few casts	0
1.014	3+	0	0	0	Few white cells	Few casts	0
1.017	3+	0	0	0	Few white cells	Few casts	0

Aorta: The intima of the aorta showed no atheromas or lipid deposits. The fibers of the media were separated throughout, apparently by edema.

Lungs: The lungs were slightly congested. The pleural surfaces were not remarkable. The increased size of the alveolar air spaces in some sections suggested slight emphysema. The bronchioles showed moderate desquamation of their epithelial cells. There was little anthracotic pigmentation in the sections studied. No tumor tissue was visible.

Mediastinal Lymph Node: The mediastinal lymph node was composed of calcified and caseous foci surrounded by hyalinized scar tissue in which anthracotic pigment was present. Outermost was a layer of vascular connective tissue in which were many leukocytes, plasma cells, polymorphonuclear leukocytes and endothelial phagocytes laden with brown and black pigment granules. This undoubtedly represented long-standing healed calcified caseous tuberculous lymphadenitis.

Spleen: The capsule of the spleen was moderately thickened by dense hyaline connective tissue. There was marked congestion of the pulp, and areas of scattered hemorrhage could be seen. About these foci were large phagocytic cells stuffed with golden brown pigment from the degenerating red cells. An increased number of polymorphonuclear leukocytes was noticed throughout.

Gastrointestinal Tract: The mucosa of the stomach showed postmortem fragmentation. The mucosal, muscular and adventitial layers exhibited the loose arrangement indicative of edema. The blood vessels were congested. There was no cellular infiltration. Other portions of the intestinal tract showed similar changes.

Pancreas: In some acini of the pancreas large foci of postmortem degeneration were present. The islet cells were not unusual in appearance. The interlobular and the interacinar connective tissue was loose and edematous.

Liver and Gallbladder: The liver capsule was of normal thickness. The hepatic sinusoids were congested throughout, but there was no cellular infiltration. Some of the endothelial cells were laden with golden pigment granules. The parenchymal cells showed early postmortem degenerative changes. In some lobules, fat vacuoles of various sizes and an increased amount of golden brown pigment within the hepatic cells were observed. The portal spaces were not remarkable.

The gallbladder showed postmortem degeneration of the mucosa. The other portions of the wall were normal.

Adrenal Glands: In the adrenal glands the cortical and the medullary cells demonstrated the changes of early parenchymatous degeneration. The interstitial connective tissue throughout was loose, edematous and congested.

Kidneys: The capsules of the kidneys were of normal thickness. There were scattered foci of sclerosis with lymphocytic infiltration here and there throughout the cortices. The glomerular capillaries were congested, and many showed proliferation and fibrosis of Bowman's capsules. In and near the scarred foci many of the glomeruli were completely changed into masses of dense hyaline connective tissue. Intermediate stages of this change also were observed. The epithelial cells of the tubules in both the cortical and medullary portions showed both postmortem and parenchymatous degeneration, and many of the cells were desquamated and lay free in the lumens. Many of the collecting tubules contained small hyaline casts. The connective tissue stroma throughout the kidneys was increased, loose and edematous. The smaller blood vessels were congested. The larger blood vessels had slightly thickened intimal coats. The renal changes were those of mild chronic vascular nephritis.

Prostate Gland: Sections from the prostate gland showed rather advanced postmortem degenerative changes. The acinar epithelium was desquamated, and the smooth muscular stroma was fragmented. The most significant change was the presence in several sections of a cellular, poorly differentiated malignant neoplasm which was not epithelial in type. Most of the tumor was necrotic, and in some spots fibrosis was marked. In those places where the cells were viable, they were observed to be small, round and hyperchromatic, resembling lymphocytes. They grew in nestlike groups. The histologic appearance and the location of the neoplasm indicated that it was not a primary prostatic tumor but rather a secondary growth which reached the prostate gland by direct invasion.

Altogether, taking into consideration the histologic and cytologic characteristics of the new growth and the gross evidence of extensive bone involvement, Dr. Conrad expressed the opinion that the tumor was primary myeloma of the lymphocytic type which had infiltrated the prostate gland from the adjacent pubic bone.

Bone: Sections from the pubic bone as well as from several ribs and vertebral bodies showed extensive invasion of the bone marrow by a primary bone marrow neoplasm. The neoplastic cells were small, shrunken and hyperchromatic, often resembling lymphocytes. They invaded and replaced the normal marrow and in places were associated with the production of much dense connective tissue. Where tumor growth was most active, fibrosis was least marked and necrosis of the tumor cells was abundant. Where growth was oldest and slowest, fibrosis was most prominent. The character of the growth was the same in all sections, although in the pubic bone there was more fibrosis than in the vertebrae or the ribs.

The tumor was considered to be primary myeloma of bone. It was of the lymphocytic type. This is the type of tumor which many European pathologists call primary lymphosarcoma of bone.

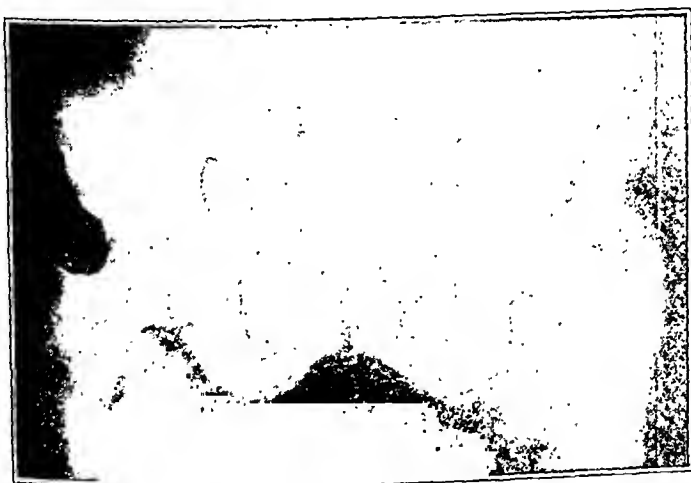


Fig. 5 (case 2).—Roentgenogram of the pelvis, showing local destruction of the superior ramus of the pubic bone on the left side and the mass displacing the bladder toward the left.

Anatomic Diagnoses.—The clinical diagnosis had been: generalized carcinomatosis of unknown origin.

The final anatomic diagnoses as approved by Dr. Arthur W. Wright were: multiple myeloma of the lymphocytic type in the pubis, the vertebrae, the ribs and the skull; secondary multiple myeloma of the prostate gland and the lungs; mild chronic vascular nephritis; cortical cysts of the kidneys; healed tuberculosis of the hilar lymph nodes; atelectasis of the lungs; anthracosis.

Report of Roentgen Observations.—Feb. 29, 1936: There was local destruction of the superior ramus of the pubic bone on the left side extending from a point $\frac{3}{4}$ inch (2 cm.) lateral to the joint of the symphysis pubis to the hip joint. There was apparently some mass within the pelvis which displaced the bladder toward the left.

March 3: After the intravenous injection of neo-iopax, the pelvis and calices of the right kidney and the right ureter were visible and apparently normal. The

calices of the left kidney were not well filled. The transverse diameter of the left kidney appeared to be somewhat greater than that of the right. The upper half of the left ureter was visible. There was no evidence of hydroureter on the left side. There was a visible defect in the bladder in its left lower quadrant.

March 4: There is no roentgen evidence of metastatic tumor in the lungs or the separate lobes.

March 5: A pyelogram of the left kidney showed the pelvis and the calices to be normal. There was no evidence of hydroureter on the left side. The lower portion of the ureter was displaced toward the midline.

June 16: The tumor formerly seen at the superior ramus of the pubis on the left side appeared to be healed. There was no definite evidence of metastatic tumor in the right femur.

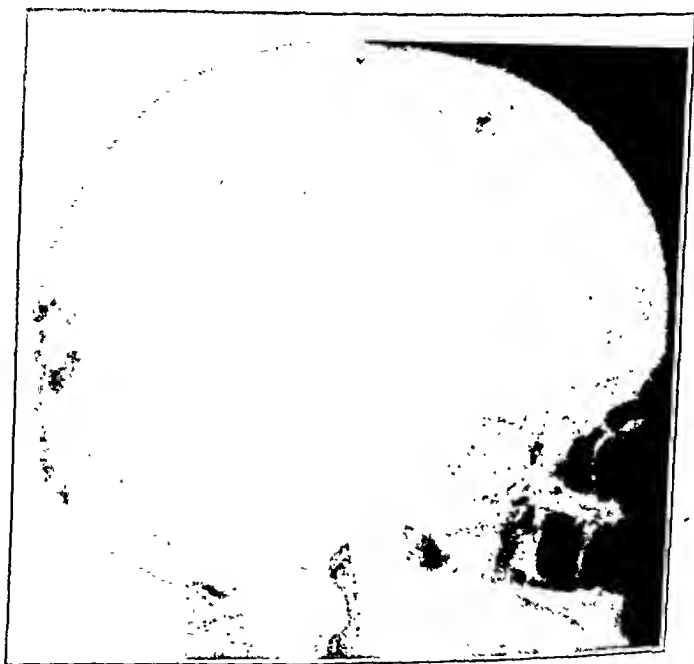


Fig. 6 (case 2).—Roentgenogram of the skull, showing large areas affected by metastatic tumor.

June 19: There were six large areas of metastatic growth in the skull. There was evidence of a metastatic tumor in the seventh rib, posteriorly on the left side.

The total dose of roentgen radiation administered was 5,550 r.

CASE 3.—H. H., a white woman 62 years of age, was first admitted to the Albany Hospital on July 22, 1934, complaining of severe pain in the lower portion of her back which radiated down to the right hip and the right leg. This pain had its onset some three months before and had not been relieved by strapping of the back. General physical examination gave an essentially negative result. The blood pressure was 140 systolic and 90 diastolic. The blood counts were normal. Chemical analysis of the blood and serologic tests gave normal results. A roentgenogram of the spine and the pelvis showed no definite pathologic

changes, although there was an increase in the lower articular portion of the body of the twelfth dorsal vertebra and the cartilage between it and the first lumbar vertebra was diminished in thickness. The only observation which it was felt might be explanatory of her symptoms was that she had unusually weak arches. She remained in the hospital for a week, and during this time arch supports were made and applied; they gave her considerable relief.

She was next admitted one month later, August 23, with the complaint of similar pain in both lower extremities, radiating from the sciatic notch down the back of the legs. Physical and neurologic examinations again yielded negative results. The blood pressure was 136 systolic and 80 diastolic. Several examinations of the blood were made, and it was found that she had a moderate amount of anemia with a persistently high color index. However, there were no findings in stained smears of the blood which could be construed as indicative of pernicious anemia. At this time the possibility of a silent growth was considered, and roentgenograms were made of the gastrointestinal tract. These disclosed no abnormalities. Since no organic disease was found to account for her symptoms, it was felt that her complaint had a neurotic basis. After rest, symptomatic care and iron therapy, her symptoms were considerably relieved, and the anemia cleared up. On September 22 she left the hospital after a month's stay with the eventual outcome still somewhat in doubt.

Approximately two months later, on November 17, the patient entered the hospital for the third time. On the morning of admission she had wrenched her right arm slightly and after this had been unable to use the member because of excruciating pain. In addition, the pain in the back and the lower extremities had recurred several weeks before and had grown steadily worse, until she had great difficulty in walking.

Physical examination at this time revealed an obvious fracture at the middle of the right humerus. The skin was rather pale. The temperature was 100 F.; the pulse rate was 98, and the respiratory rate was 22. The blood pressure was 90 systolic and 58 diastolic. There were impaired resonance, increased whisper in speaking and moist rales at the base of the left lung in the midaxillary line. Active and passive motion caused severe pain in the lower lumbar region and the legs. No neurologic changes were found.

The urine for the first time showed large amounts of albumin and a few white blood cells. Blood counts were within normal limits.

Roentgenograms revealed fractures through the middle of the shaft of the right humerus, the ninth rib on the right side and the sixth, seventh, ninth and tenth ribs on the left, with evidence of a metastatic tumor in the ribs on both sides of the chest. There was evidence of thickening of the pleura on the left side toward the mediastinum about the apical portion of the lung; this thickening might have been due to neoplastic invasion or to effusion along the medial aspect of the lung. There was a partial collapse of the eighth dorsal and fourth lumbar vertebrae, and there was evidence of a metastatic tumor in the shaft of each femur just below the lesser trochanter.

The fracture of the right humerus was reduced and a molded plaster splint applied. Because of pain in the back and weakness, which now became apparent, the patient remained bedfast during the rest of her stay in the hospital. About three weeks after admission she began to complain of numbness and tingling of the feet and difficulty in moving the lower extremities. Neurologic examination at this time showed that active motion of the lower extremities was entirely lacking and that there was great diminution of muscle strength throughout both legs.

TABLE 8.—Data on Patient in Case 3

Date	Wasser- mann Tests	Blood Pressure, mm. of Mercury	Hemo- globin, per Cent	Blood Counts										Blood Chemistry				Notes
				Red Blood Cells	White Blood Cells	Poly- morpho- nuclears	Eosino- phils	Differential		Unde- rlined	Non- protein Nitrogen, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Cyst. Mg. per 100 Cc.	Protein per 100 Cc.				
								Lympho- cytes	Myelo- cytes									
7/22/34 (1st admission)	..	140/90	89	4,430,000	8,600
7/23/34
7/24/34
7/27/34
8/24/34 (2d admission)	80	3,200,000	4,800
8/25/34	..	136/80
8/26/34	83	3,250,000	5,200	67	..	31	2
8/28/34	88	3,800,000	5,000
9/ 3/34	93	4,090,000	8,200	62	1	35	2
9/ 5/34	101	5,150,000
9/ 9/34	100	4,170,000
9/16/34	101	5,070,000
11/17/34 (3d admission)	..	90/58
11/18/34	..	105/60	81	4,200,000	9,200	65	2	20	10	3
11/20/34
11/21/34
11/24/34
12/ 3/34	70	3,900,000	10,020	68
12/13/34
12/15/34	63	3,000,000	8,900
12/15/34	63	3,000,000	8,900
12/15/34	63	3,000,000	8,900
12/15/34	63	3,000,000	8,900
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12/15/34	63	3,000,000	8,900
12/15/34	63	3,000,000	8,900
12/15/34	63	3,000,000	8,900
12/15/34	63	3,000,000	8,900								

The knee jerks were diminished, and the ankle jerks could not be elicited. No pyramidal tract signs were present. There was normal sensitivity to touch. Sensation of pain was diminished over the right foot. The muscles of the calf were insensitive to deep pressure. Sense of vibration was entirely absent over the patellas, the shins and the malleoli. Sense of position was impaired bilaterally, more on the right. Heat and cold could not be discriminated over the right foot.

After this the patient's course was rapidly downhill. She had difficulty in starting urination and had to be catheterized constantly. Constipation was marked, and daily enemas were necessary. Increasingly large doses of morphine were required to control the inordinate pain. After several more weeks she complained of girdle pains across the abdomen and showed a definite level of hyperalgesia and hyperesthesia just below the umbilicus. There was increasing respiratory difficulty. The blood pressure was 105 systolic and 60 diastolic. She grew steadily weaker; the erythrocyte count and the hemoglobin value fell markedly, and death ensued on December 27, some six weeks after admission and eight months after onset.

A culture of the patient's blood on this date showed overgrowth by spreader.

Autopsy (Dr. G. H. Klinck Jr.).—The body was that of a white woman 63 years of age, 60 inches (150 cm.) in length, normally developed but undernourished. The body was warm and flaccid. There was slight lividity of the dependent portions. No edema was observed. The skin was pale and thin. The hair was brown and plentiful. The ears and nose were normal. The eyes were brown; the pupils were equal, regular and middilated. The membranes of the mouth were covered with a dirty mucoid material. All teeth were absent. The right arm was in a rather loosely fitted splint consisting of small pieces of wood and bandage. The finger tips were cyanotic. The breasts were of moderate size and free from palpable masses. Sections revealed nothing of note. The abdomen was large but not distended. There was an ecchymotic area, 4 cm. in diameter, over the anterosuperior spine of the ilium on the right. The body was opened by the usual autopsy incision. On reflecting the muscles from the thorax it was noted that the ribs were soft and supported numerous hemorrhagic soft nodules, 0.5 to 1.5 cm. in size. These were slightly raised. The muscles were of a good red color and were moist. The thoracic fat measured 1 cm. and the abdominal fat 2 cm. in thickness.

The peritoneal cavity was free from fluid and adhesions. The diaphragm reached the level of the fifth rib on the left and the fourth rib on the right. The great omentum was large, moderately fatty and showed a few small red nodules, 3 mm. in diameter. These nodules were similar to other tumor nodules already described. The mesenteric fat was plentiful. There were numerous nodules in the mesentery which varied between a few millimeters and 1.5 cm. in diameter. It was presumed that they represented tumor growths in lymphoid tissue. Toward the periphery of the mesentery the nodules were small. In the midportion and the root of the mesentery the nodules were large, the largest being 1.5 cm. in diameter. These masses were composed of extremely soft friable dark red hemorrhagic tissue. A few appeared to be encapsulated, but in most the hemorrhagic tissue appeared to be invading the fat of the mesentery. Two nodules, 1 cm. each in diameter, were attached to the peritoneum lining the pelvis. These nodules projected above the surface but were not pedunculated. Like all others, they were soft, friable and hemorrhagic. A portion of one of these was pale and firm. It probably represented a more recent growth. The peritoneal surfaces were generally smooth, glistening and moist.

Each pleural cavity was free from fluid. The visceral pleura in each was smooth and glistening. The parietal pleura covering the ribs presented an irregular appearance because of underlying tumor nodules arising from the ribs. These nodules elevated the parietal pleura about 0.5 cm. in each instance. The presence of these dark red tumor masses caused great irregularity of the thoracic cage.

In the mediastinum a few anthracotic lymph nodes were present. There were no tumors similar to those previously described.

The pericardial cavity was free from adhesions. It contained the usual amount of clear yellowish fluid. The epicardial surfaces were smooth and glistening. There was somewhat less than the usual amount of subepicardial fat. The coronary arteries were slightly thickened but tortuous. The heart was soft but free from dilatation. The myocardium was of a good red color and showed no areas of softening or fibrosis. The endocardium was smooth throughout. The valve leaflets showed no essential changes. The foramen ovale was closed. The heart weighed 310 Gm. The circumferential measurements of the valves were as follows: tricuspid valve, 11 cm.; pulmonic valve, 7 cm.; mitral valve, 9.5 cm.; aortic valve, 8. The myocardium of the left ventricle measured 1.5 cm., that of the right ventricle, 0.5 cm.

In all portions of the aorta there was marked atherosclerosis.

The left lung weighed 265 Gm. The upper lobe was soft, gray and crepitant throughout. On section the tissue was dry and vesicular. Scattered diffusely throughout were a few bright red circumscribed areas which probably represented bleeding from the severed ends of blood vessels. The lower lobe was extremely small, grayish red, fleshy and noncrepitant. No definite tumor masses could be made out by palpation. On section the lung substance appeared grayish red and fleshy. Scattered here and there were a few slightly elevated hemorrhagic areas, which were but slightly firmer than the surrounding lung substance. These areas varied between a few millimeters and 1 cm. in diameter. They were poorly circumscribed and blended readily with the surrounding lung substance. Some of the larger areas appeared to be made up of collections of similar hemorrhagic areas. From gross examination it could not be said whether these reddish areas represented pneumonia or secondary tumor. The arterial tree was normal. There was no evidence of neoplasm in the bronchial tree.

The right lung weighed 260 Gm. The upper, middle and lower lobes were soft, gray and crepitant throughout. On palpation no nodules could be felt. On section numerous small hemorrhagic areas were seen scattered throughout all lobes. In the lower lobe these were fairly prominent and slightly firmer than in the others. As in the examination of the left lung, the question arose as to whether they represented neoplasm or foci of pneumonia. The arterial and bronchial trees were carefully examined and found normal.

The spleen weighed 180 Gm. It was free from adhesions. It was large, soft, dark red and flabby. When sectioned, it showed a soft, almost semifluid pulp which was finely mottled gray and red. The trabeculae were not increased in size. The follicles were difficult to differentiate. The pulp was homogeneous throughout, and there was no evidence of neoplasm.

The stomach was small, contracted and empty. The mucosa was pink, smooth and free from neoplasm. The lower portion of the esophagus was attached to the stomach and showed nothing of note. The small intestines were collapsed and empty. The mucosa was slightly congested in the same portions but not to a marked degree. A somewhat pedunculated firm nodule, 0.4 cm. in diameter, was found in the midportion of the ileum, beneath the mucosa. It appeared to

be a mass of lymphoid tissue. The appendix was not remarkable. The large intestine contained much fecal material, and the mucosa was slightly congested. No evidence of neoplasm was found in any portion of the gastrointestinal tract.

The pancreas was small and atrophic. There was some fatty infiltration. The pancreatic tissue proper was pale and firm.

The liver weighed 1,610 Gm. It was large. The surfaces were smooth and the edges sharp; the color was brownish red. Section revealed a finely mottled, reddish gray parenchyma. The finer markings were distinct. The tissue had a rather opaque appearance. The cut edge everted, and the parenchyma bulged to a slight extent.

The gallbladder measured 10 by 4 cm. It was thin walled and contained much thin green bile. There were no stones, and all the ducts were patent.

The right adrenal gland was not remarkable. The left adrenal gland was compressed but otherwise unchanged by a tumor mass 2 by 2 by 1 cm. which lay close to it. The tumor was composed of friable hemorrhagic tissue, which was sharply circumscribed.

The left kidney weighed 160 Gm. It was large, firm and free from congestion. The capsule stripped easily and displayed a relatively smooth pinkish gray surface which was free from scars. Section revealed a pale cortex which averaged 1 cm. in thickness. The cortical portions were sharply demarcated from the medullary portions. The large vessels showed only slight thickening. The pelvis was normal. The right kidney weighed 165 Gm. It was similar to its fellow.

The bladder was small, contracted and empty. The mucosa was rugose and was of a pink color. The walls of the bladder were thick.

The tubes and the ovaries showed the usual atrophic changes. Attached to the under surface of the left ovary there was a mass of hemorrhagic neoplastic tissue 1 cm. in diameter. It appeared to be growing outside of and compressing the ovary. The uterus was small and contained a single leiomyoma, 2 cm. in diameter, in the fundus. The cervix was small and partially occluded. The mucosa of the uterus presented several rather firm small polyps. One of these was cystic. These polyps were obviously benign.

The scalp was incised in the usual manner and reflected. The bones of the cranium will be described along with the skeleton in general. The calvarium was cut and removed. The dura was of normal thickness and did not bulge.

The brain weighed 1,300 Gm. The brain in situ was symmetric. The arachnoid vessels were slightly congested. The convolutions and the sulci were of normal proportions. After removal, the brain was symmetric. There was slight atherosclerosis of the large vessels at the base. The cerebellum and the medulla appeared normal. The attached portion of the cervical cord was not remarkable. There was no external evidence of tumor. The brain was set aside for hardening and future study.

The pituitary gland was small and congested but otherwise normal.

The linings of both ethmoid sinuses were easily removed. In the posterior portion of each there was a growth of dark red hemorrhagic tumor, measuring 0.5 cm. in diameter. These growths were symmetric and were attached to the outer surfaces of the base of the sella turcica, which contained neoplasm and which will be described later.

The greater portion of the spinal cord was removed by the abdominal route. The cord was normal as far as could be determined down to the level of the fourth thoracic vertebra. From this point downward the substance of the cord

was amorphous, soft and white. When the cord was sectioned, the substance of the softened cord could be squeezed from the surrounding arachnoid membranes. No structural pattern was visible in these softened portions. No sharp line of demarcation could be found between the softened and the unchanged portion of the cord. No cause for this softening could be found by gross examination.

Segments of the large lumbar nerves were taken for study. The thyroid gland was small and symmetric. A small piece was taken for study.

In the calvarium there was a red hemorrhagic soft area, 1.5 cm. in diameter. It was located slightly to the left of the midline in the anterior portion of the left parietal bone. It extended completely through the thickness of the calvarium. A few similar areas, 0.3 cm. each in diameter, were observed in the most prominent portion of the right side of the frontal bone. After the brain was removed, the dura was stripped from the base of the skull. There was a softened hemorrhagic area in the bone; this formed the roof of the anterior portion of the left orbit. This area measured 1 cm. in diameter. Another softened hemorrhagic area was observed in the central portion of the left middle cerebral fossa. After the pituitary gland was removed, it was noted that almost the entire base of the sella turcica was soft, hemorrhagic and crumbly.

The sternum presented no projecting tumors, but a medial section showed that there was great softening of all portions of the sternum. The cortices of the bones were thinned out and soft. The cancellous portions were largely replaced by a soft hemorrhagic tissue. The sternum bent and fractured easily.

Every rib presented irregular tumefactions, 0.5 to 1.5 cm. in diameter. These swellings were raised to the extent of 0.5 cm. They were extremely numerous and in some instances were closely set. They were present in the anterior and the posterior portions of the ribs and were observed on the external as well as on the internal surfaces. Some of the tumors extended into the surrounding muscles. There were no ulcerations of the parietal pleura. The ribs were soft and fractured easily. Sections showed that the tumors replaced the bony structures as well as the marrow spaces. The tumors were soft, friable and hemorrhagic. All the rib marrow was extremely soft and red, probably owing to replacement by neoplasm.

The vertebral column was examined as far as possible. In all portions a replacement of the cancellous bone and sometimes of the cortex by soft hemorrhagic tumor was observed. The neoplastic process was most marked in the lumbar segments but was distinctly visible as high as the third thoracic segment. In the lumbar region the vertebral segments were reduced to a mere soft red jelly. The interior vertebral disks were soft, apparently edematous and greatly swollen. Some of them measured 1.4 cm. in thickness.

Numerous sections of the right ilium were made. The bone marrow showed no changes as far as investigated.

The right femur was examined in its midpoint. After the muscles had been stripped away, the bone presented a mottled hemorrhagic appearance. It cut with some ease. The segment of the cortex was lifted off, and it was observed that the cortex was greatly thinned out owing to invasion by neoplasm similar to that described before. The marrow spaces contained large quantities of soft, almost jelly-like dark red tumor.

There was a pathologic fracture in the right humerus at the junction of the middle and the upper third. There was some palpable tumefaction at this point, and crepitus was noted. The site of fracture was examined. There was only

slight evidence of the formation of callus. The fractured ends of the bone were ragged and soft and showed marked neoplastic invasion. The cortical portions of the bone were thinned out and the marrow cavity contained soft red tumor.

The provisional anatomic diagnoses were: multiple myeloma involving the skull, the spine, the ribs, the sternum, the humerus and the femur; secondary myeloma of the abdominal lymph nodes; secondary myeloma of the lung (?); early bilateral bronchopneumonia; atelectasis of the lower lobe of the left lung; leiomyoma of the uterus; benign endometrial polyps; atherosclerosis of the aorta.

Examination of the Brain After Hardening in Formaldehyde Solution (Dr. G. H. Klinck Jr.).—The external appearance of the brain was similar to that of the organ when fresh. The brain was examined by making numerous parallel frontal sections. These sections revealed that the normal patterns of white and gray matter were present. There were no areas of softening or hemorrhage. The ventricles were of normal size, and their linings appeared smooth and glistening. Sections through the pons varolii, the cerebellar hemispheres and the medulla showed no remarkable changes.

Microscopic Examination.—Heart: The epicardium was not remarkable except for the fact that it contained a large quantity of fat. The branches of the coronary artery showed a moderate degree of thickening. The branches deep within the heart muscle were surrounded by an increased amount of fibrous connective tissue. The endocardium showed slight thickening in a few places. The fibers of the heart muscle were in general well preserved but in a few places they were being replaced by fibrous connective tissue. A moderate number of fibers of the heart muscle were much larger than normal.

Two poorly circumscribed collections of atypical cells were observed within the myocardium. These cells were generally round in outline, and many of them appeared to be plasma cells. A number of cells containing multiple nuclei were observed. It was believed that these cells were identical with those found in the tumors located in the other portions of the body.

Aorta: One section of the aorta showed a moderate degree of hyaline thickening of the intima. The media and the adventitia were not remarkable.

Lungs: Numerous sections of the lungs were studied. The pleural surfaces showed nothing worthy of note. Marked congestion of almost all the pulmonary vessels was observed. In many of the sections numerous air sacs were filled to capacity with large amounts of fibrin, polymorphonuclear leukocytes and mononuclear phagocytes. Occasional round cells also were present in the exudate. Many air sacs contained large amounts of finely granular acidophilic material, which was doubtless precipitated protein of edema fluid. All branches of the bronchial tree contained large amounts of degenerating inflammatory exudate. This exudate consisted of fibrin and debris. In some of the branches of the bronchial tree the exudate also contained large numbers of small round cells appearing to be lymphocytes. In some sections there was a moderate degree of fibrosis of the lung substance. Further examination failed to disclose the presence of any secondary tumor nodules.

Spleen: The capsule of the spleen was slightly thickened. The splenic follicles were few and small. The central portions of many of these follicles contained deposits of dense hyaline material. Some of the splenic sinuses were moderately congested; others were markedly congested. The pulp appeared unusually cellular. This appearance was due to the presence of enormous quantities of plasma cells. These cells much resembled the plasma cells found in the tumor nodules previously described. There were no localized growths of tumor cells.

Pancreas: In the pancreas a moderate degree of fatty infiltration was observed. There was a slightly increased amount of interacinar fibrous tissue. The acinar cells showed no unusual changes. The islet cells appeared normal, and the islets were normal in number. No secondary tumor masses were observed.

Liver: The liver cells were swollen and granular and lacked definite cell outline. The cells in the central portions of the lobules showed a moderate degree

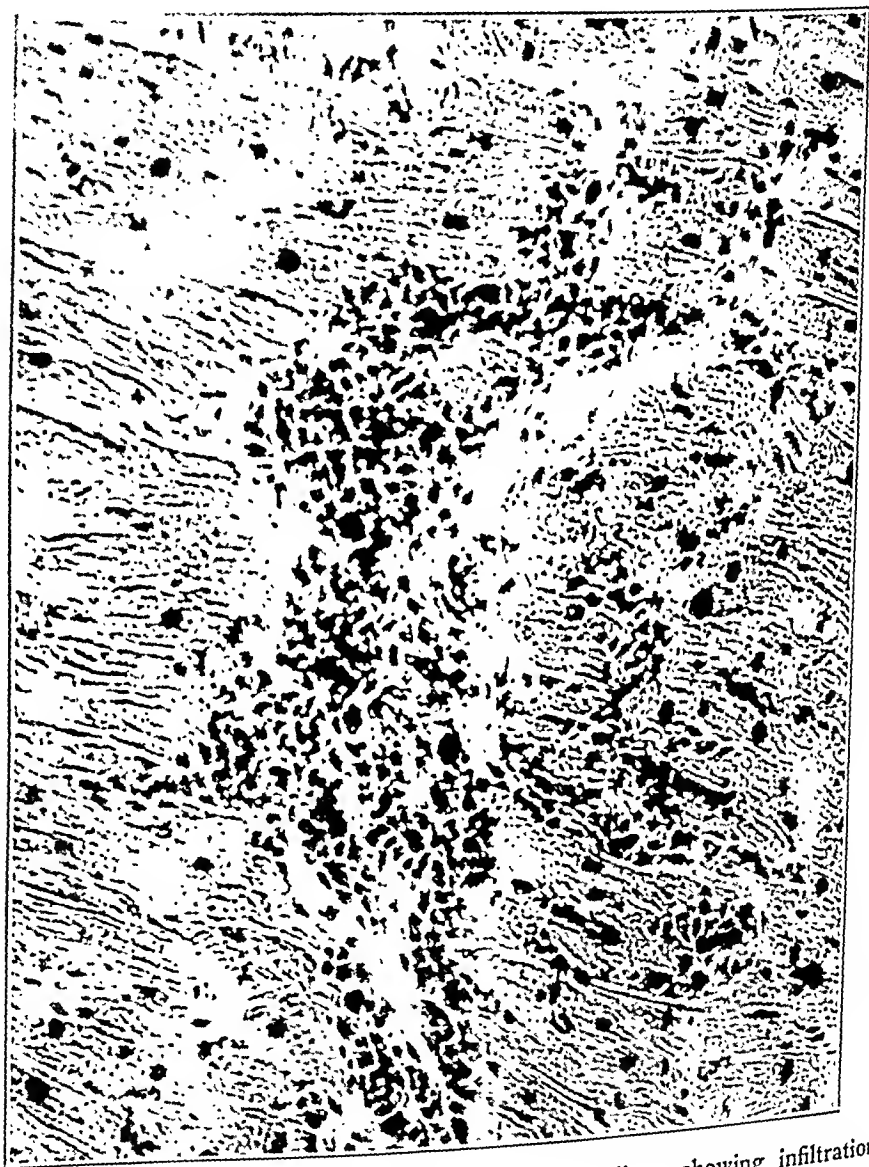


Fig. 7 (case 3).—Photomicrograph of the myocardium, showing infiltration of mononuclear and multinuclear cells similar to tumor cells found elsewhere in the body.

of parenchymatous degeneration. Actual necrosis was not observed. All the sinuses of the liver were large and contained innumerable cells. In addition to erythrocytes and debris there were large numbers of round cells present. Many of these were definitely plasma cells; they resembled the cells found in the tumor nodules described elsewhere. In addition to these cells there were also numerous

rather small multinuclear giant cells. These cells were of the same type as those found in the secondary tumor masses previously described. No definite circumscribed collections of tumor cells were observed in any sections of the liver studied. A large number of lymphocytes were found in the periportal fibrous tissues. The significance of myeloma cells in the sinuses of the liver was not clear.

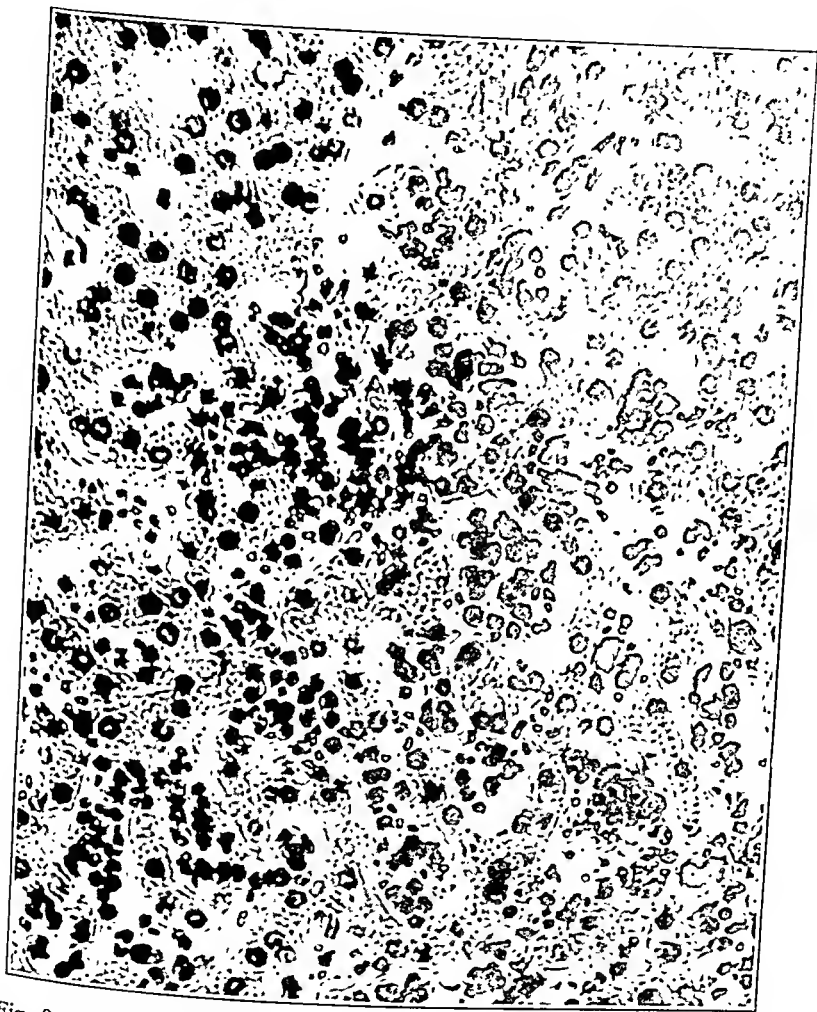


Fig. 8 (case 3).—Photomicrograph of a section of the liver. The sinusoids of the liver contained large numbers of tumor cells similar to those found elsewhere in the body. Many multinucleated cells are shown.

Adrenal Gland: A section of one adrenal gland showed no remarkable changes. Adjacent to the glandular tissue there was a large mass of secondary myeloma. This neoplastic tissue was identical with that already described.

Kidneys: The branches of the renal artery showed a moderate degree of thickening. This was most conspicuous in the large and the medium-sized

branches. Occasionally, hyalinized glomeruli were observed; other glomeruli were congested but showed no remarkable changes. There was marked swelling, cloudiness and granularity of the epithelium of the convoluted tubules. Many of these cells lacked definite cell outlines. Between some of the tubules there was an increased amount of fibrous tissue. No tumor cells were observed in any of the sections studied.

Bladder: Sections of the bladder showed that the mucosa was well preserved and that there was nothing unusual about the muscle coats.

Genitalia: A section of the uterus revealed the presence of a large endometrial polyp. The glands in this polyp were small, but the stroma was exceedingly dense. The stroma cells were oval and appeared to be of the normal type, but they were unusually numerous.

Ovary: The ovarian tissue was normal appearing. Attached to one pole of the ovary there was a mass of neoplasm. The tissue was loose in texture, exceedingly vascular and extremely hemorrhagic. The bulk of the tumor was composed of large numbers of round cells of the plasma cell type. A moderate number of tumor giant cells were also present.

Retroperitoneal Tumor Mass: In the periadrenal fat a large mass of secondary tumor was observed. This tumor tissue was extremely vascular and markedly congested. The bulk of the tumor consisted of large numbers of plasma cells and round cells which did not show the typical characteristics of plasma cells. In addition there were numbers of tumor giant cells containing between three and four nuclei. Little cytoplasm was observed in these cells.

Thyroid Gland: The acini were large and filled with colloid substance. The acinar cells were considerably flattened. The picture was that of a somewhat underactive gland.

Bone Marrow: Sections of the bone marrow from the vertebra, the sternum, the ribs, the femur and the skull were studied. In general, sections from the various portions showed essentially the same changes. Normal bone marrow was only occasionally recognizable; the bulk of the marrow was replaced by an overgrowth of cells characteristic of myeloma. The cell which appeared most frequently was a fairly typical plasma cell. This cell was large and had an ovoid or round nucleus in which the chromatin material was arranged in radiating bands like the spokes of a wheel. All of the nuclei contained nucleoli. The cytoplasm of these cells varied in amount and was generally clear. Numerous cells containing two or four nuclei were observed. These nuclei were generally similar to the ones occurring in the mononuclear cells. Another type of cell, somewhat smaller than the plasma cell, was observed; it was round or ovoid and had a rather dense nucleus and relatively little cytoplasm. Numerous transition forms between the two cell types were observed. In all instances the myeloma tissue was extremely vascular; the vessels were usually markedly congested, and large numbers of erythrocytes could be seen in the tissue spaces. There was relatively little supporting stroma in the tumor masses. It could be seen that the cortical portions of bone were being eroded by adjacent tumor. A section of rib showed that the myeloma tissue had extended completely through the cortex and was infiltrating the adjacent soft tissues.

Fractured Ends of Right Humerus: Sections from the fractured ends of the right humerus showed the presence of large amounts of myeloma tissue in bone and adjacent fat tissues. Attempt at repair of this was indicated by the presence of relatively small amounts of rather loose fibrous tissue containing large numbers of recently formed blood vessels. In all portions there was much hemorrhage.

Degenerating bits of bone could be seen near the site of the fracture. A small amount of recently formed bone was observed.

Intervertebral Disks: Sections of these disks revealed a vascular loose edematous fibrous connective tissue which showed signs of degeneration.

Brain: Sections of cerebral tissue showed that the vessels in the arachnoidal spaces had walls of normal thickness and were free from inflammatory reaction.

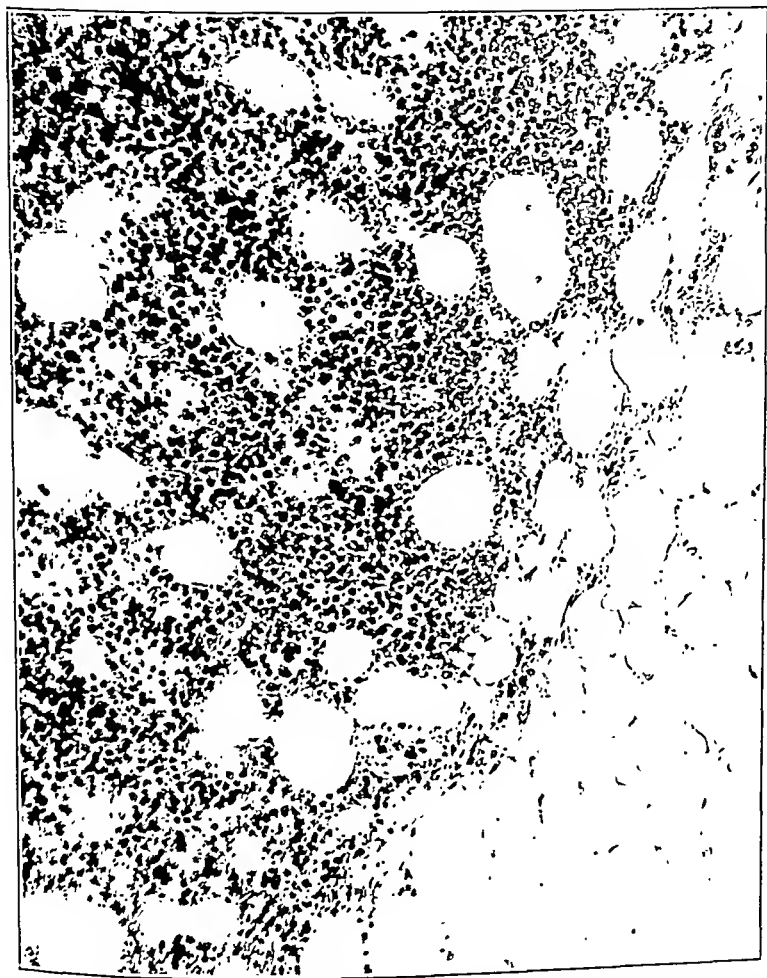


Fig. 9 (case 3).—Photomicrograph of a section of retroperitoneal fat, showing extensive infiltration of tumor cells. Mononuclear and multinuclear cells are shown invading the fat.

Sclerosis of the subarachnoidal tissues was present in a mild degree. The vessels in the brain tissue showed moderate congestion and dilatation of the perivascular lymph spaces. The cerebral substance proper showed nothing extraordinary. The choroid plexus was normal in appearance and showed few foci of calcification. No inflammatory reactions were observed in any portions of the brain studied.

Spinal Cord: Sections from the cervical portion of the spinal cord showed no unusual changes. Various sections from the softened portion of the cord revealed extensive degenerative changes. In almost all these sections the cord substance was reduced to a loose syncytial-like mass of degenerating nerve tissue containing a moderate number of mononuclear phagocytes filled with lipoid material. This condition obtained from the upper portions of the softened area down to the filum terminale. In these sections it was observed that the nerve trunks leaving the spinal cord also showed marked degenerative changes.

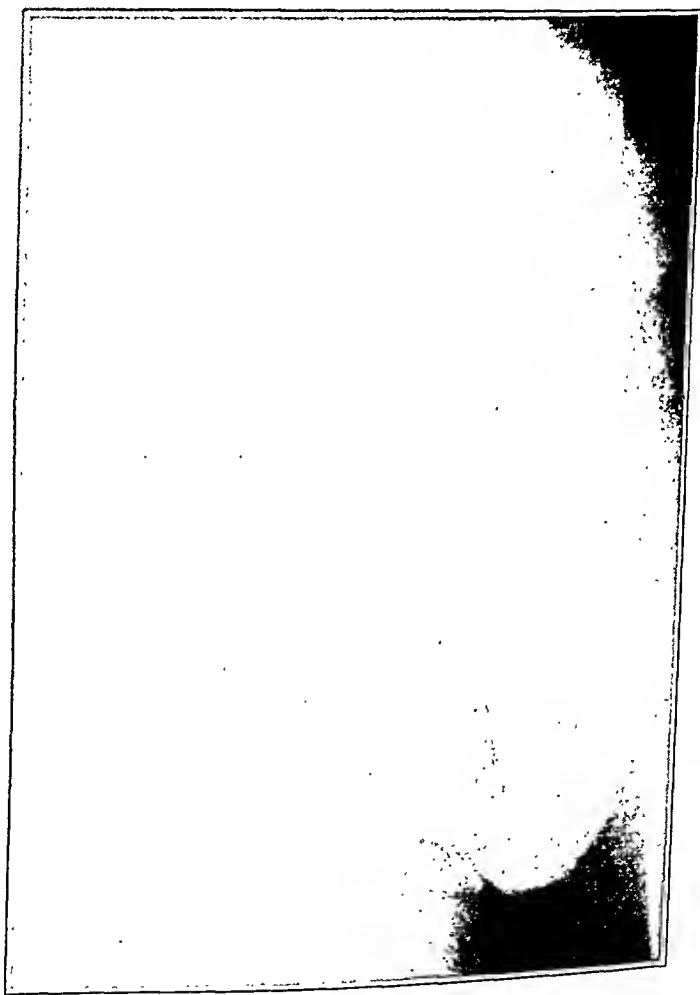


Fig. 10 (case 3).—Roentgenogram showing fracture in the right humerus; the fracture is in end to end contact, and there is a slight degree of angulation.

In a section taken from the lower portion of the spinal cord it was noted that copious hemorrhage had occurred. The tissues in and around the region of the hemorrhage contained many polymorphonuclear leukocytes. The hemorrhage apparently was old. No indication of the cause of the softening could be had from the sections studied or by gross examination. The larger vessels of the pia arachnoid showed moderate thickening of their walls.

Pituitary Gland: Section of the pituitary gland revealed no abnormalities.

Report of Roentgen Observations.—July 23, 1934: There was an increase of density in the lower articular portion of the body of the twelfth dorsal vertebra. The cartilage between this and the first lumbar vertebra was diminished in thickness. There were no arthritic changes in the tenth and eleventh dorsal or in any of the lumbar vertebrae. The sacroiliac joints and the hip joints appeared normal. The fifth lumbar vertebra was in normal relation to the sacrum.

August 27: The large bowel filled normally. Normal markings were visible throughout the course of the colon. There were no constrictions or filling defects. The esophagus was normal; the stomach was of the steer horn type and was



Fig. 11 (case 3).—Roentgenograms showing metastatic tumors in the shaft of the femur.

normal in size, shape and position. The outline of the stomach and the cap was normal. There were no defects suggesting ulceration or new growth. In six hours the stomach was empty. The barium sulfate was accumulated in the terminal portion of the ileum and in the ascending colon.

August 28: In twenty-four hours the barium sulfate filled the ascending, the transverse and the proximal half of the descending colon.

November 17: There was fracture through the middle of the shaft of the right humerus. There was evidence of fracture through the ninth rib on the right side.

November 19: After the application of a molded plaster splint, a fluoroscopic examination of the right arm disclosed the fracture in end to end contact. There was a slight degree of angulation.

Spinal Cord: Sections from the cervical portion of the spinal cord showed no unusual changes. Various sections from the softened portion of the cord revealed extensive degenerative changes. In almost all these sections the cord substance was reduced to a loose syncytial-like mass of degenerating nerve tissue containing a moderate number of mononuclear phagocytes filled with lipid material. This condition obtained from the upper portions of the softened area down to the filum terminale. In these sections it was observed that the nerve trunks leaving the spinal cord also showed marked degenerative changes.

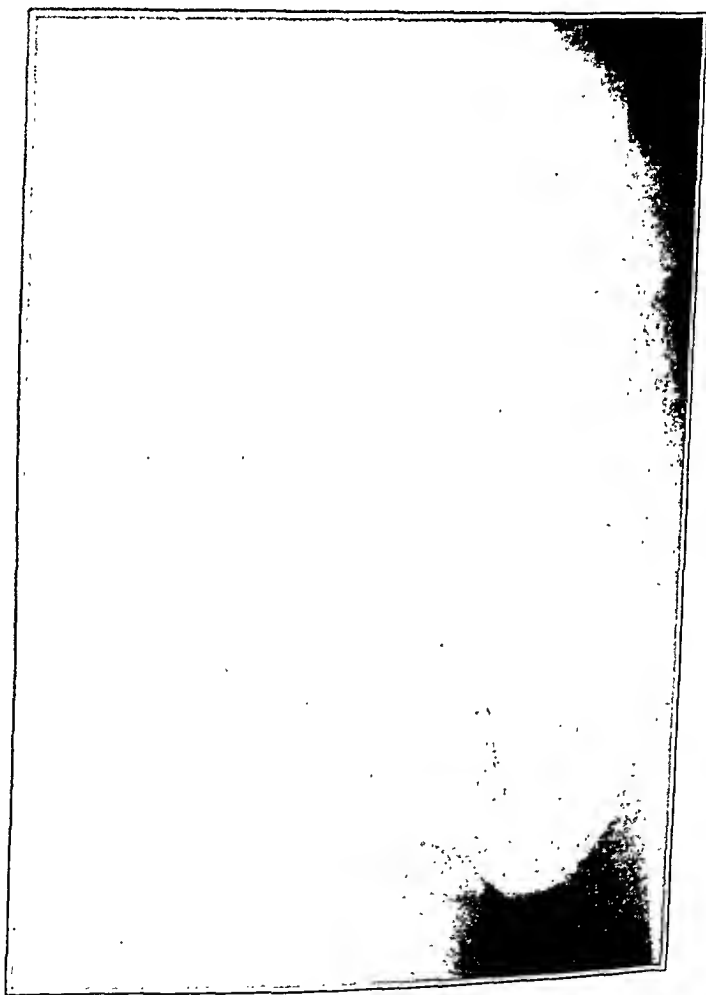


Fig. 10 (case 3).—Roentgenogram showing fracture in the right humerus; the fracture is in end to end contact, and there is a slight degree of angulation.

In a section taken from the lower portion of the spinal cord it was noted that copious hemorrhage had occurred. The tissues in and around the region of the hemorrhage contained many polymorphonuclear leukocytes. The hemorrhage apparently was old. No indication of the cause of the softening could be had from the sections studied or by gross examination. The larger vessels of the pia arachnoid showed moderate thickening of their walls.

Pituitary Gland: Section of the pituitary gland revealed no abnormalities.

A roentgen examination made before the patient left the hospital showed in addition to the observations already noted erosion of the third lumbar vertebra, of the right wing of the sacrum and of the left acetabulum.

A probable diagnosis of metastatic tumor was made. No primary lesion was found. Alcohol introduced intraspinaly gave some relief from pain. High voltage roentgen therapy was instituted but stopped because of the extreme nausea and vomiting which followed each treatment.

On September 17, the patient reentered the hospital, having had a progressively downhill course during the few weeks away from the hospital. The pain had continued unabated. For about one week prior to admission she had become progressively short of breath, and her legs and ankles had become greatly swollen.

At the time of this admission there was little change in the results of physical examination, except for the swelling of the legs and the ankles. Numerous moist bubbling rales were heard at the bases of both lungs; the respirations were rapid and shallow.

The blood pressure was 80 systolic and 60 diastolic. The temperature was 98 F.; the pulse rate was 160; the respiratory rate was 48.

The urine showed a trace of albumin; otherwise it was normal.

The hemoglobin content had dropped to 52 per cent; the differential count was not indicative of any change in the blood.

On the fourth day after admission, the breathing became more rapid and labored and the pulse extremely rapid. The legs and the abdomen were tremendously edematous and tender to the touch. On several occasions death seemed imminent, but the patient rallied. Finally, the respirations became much more irregular, and the patient died within a few minutes.

The diagnosis made was possible multiple myeloma or secondary carcinoma.

Unfortunately, no chemical examinations were made.

Report of Roentgen Observations.—July 13, 1935: There was no roentgen evidence of metastatic tumor in the skull, the lungs or the ribs.

August 2: There was evidence of destruction and collapse of the tenth dorsal vertebra, suggesting metastatic tumor. There was no evidence of metastatic tumor in the cervical vertebrae. Further examination showed erosion of the third lumbar vertebra, of the right wing of the sacrum and of the left acetabulum.

Autopsy.—The body was that of a well developed and well nourished obese Italian girl, 24 years of age. The length of the body was 134 cm. Rigor mortis was not present. There was livor mortis of the dependent portions. There was marked pitting edema of both lower extremities, and there was moderate edema of the hands and the flanks. The surfaces of the skin were smooth and moist and showed no eruption. The hair was long and black. The ears and the nose were normal. The pupils were equal, round and regular and were mid-dilated, measuring 0.4 cm. in diameter. Two large vaccination scars were present on the left upper arm. The abdomen was large and rotund, and the skin showed many striae.

The panniculus adiposus measured 2 cm. in thickness. The subcutaneous tissues were moderately edematous, but no fluid was present in the peritoneal space itself. The mesothelial surfaces were smooth, moist and glistening. No adhesions were present. The diaphragm was at the level of the seventh rib on the left and at the level of the sixth interspace on the right. The inferior vena cava was thrombosed.

Inasmuch as the autopsy incision was limited to the abdomen, the heart and the lungs were removed through the diaphragm; accurate inspection of these cavi-

ties was therefore not possible. However, no excessive fluid was observed, and the surfaces appeared smooth, pale and glistening. No adhesions could be palpated.

The heart weighed 220 Gm. It appeared small for the weight of the patient. The myocardium was meaty red and flabby. It measured 0.5 cm. in thickness in the left ventricle and 0.2 in the right. The coronary arteries disclosed nothing of note. The left ventricle showed flattening of the trabeculae carneae and appeared relatively enlarged. However, the valve rings had normal circumferences: the tricuspid, 10 cm.; the pulmonic, 5 cm.; the mitral, 9 cm.; the aortic, 5 cm. The endocardium of the valve leaflets and throughout the chambers of the heart showed nothing of note.

In the aorta there were no noteworthy changes. In places the vessel was rather small, apparently from compression by adjacent tumor tissue.

The right lung weighed 280 Gm. and the left 250 Gm. Each was pinkish gray and spongy. On the costal surface of the middle lobe of the right lung was a firm whitish nodule, 3 cm. in diameter and extending 0.8 cm. into the lung substance. On section this tissue was firm and whitish and appeared highly cellular. It was not encapsulated. The remainder of the lung showed nothing of note.

The left lung, like the right, had smooth pleural surfaces. It contained a single elongated spoon-shaped deep reddish raised focus, 11 by 1 cm. in size and extending 1 cm. into the lung substance. Its cross section was roughly wedge shaped, typical of a hemorrhagic infarct. The remainder of the lung was pinkish, spongy and crepitant throughout. There was no evidence of a pneumonic process.

The spleen weighed 230 Gm. It was firm in consistency, and its capsule was smooth and deep purple. On section the pulp was solid and deep purplish red. The lymphoid follicles were not prominent.

The esophagus and the stomach showed nothing of note. Grossly, the small intestine, the appendix and the large intestine were normal.

The pancreas showed nothing of note.

The liver was enlarged and weighed 2,100 Gm. It was yellowish brown and mottled and on section presented yellow greasy speckled cut surfaces. Serial sections yielded no evidence of tumor nodules in the parenchyma.

The gallbladder was thin walled and contained about 40 cc. of thick yellow bile. The ducts were patent.

The adrenal glands showed nothing of note.

The right kidney weighed 290 Gm. It was buried in a large mass of fat which was infiltrated with white neoplastic tissue that was present retroperitoneally along the margin of the spinal column. On section the perinephric fat was seen to be invaded by white cellular tumor tissue and was adherent to the capsule of the kidney over its lower three quarters. About a dozen small round white cellular nodules were present in the renal cortex itself. These nodules averaged 0.3 cm. in diameter. The pelvis was dilated, and its walls had the appearance of ground glass. The cortex itself was pale and yellowish white with many yellowish lines which radiated from the pelvis outward. The medulla was likewise pale, and the corticomedullary junction was indistinct. The ureter was embedded in a mass of fat and tumor tissue. A fine probe was passed through its lumen only with considerable force.

The left kidney weighed 240 Gm. It was pale and flabby. Its capsule was smooth and stripped with ease. On section the cortex and the medulla were pale yellowish with whitish radiating streaks similar to those in the right kidney. The corticomedullary junction was indistinct. Three small tumor nodules similar

to those in the right kidney were present in the cortex. The pelvis was slightly distended. The ureter was patent.

The bladder showed nothing of note. A small amount of clear yellow urine was present.

The uterus, the tubes and the ovaries were not remarkable. The veins of the broad ligament on the right side were thrombosed.

Practically all of the retroperitoneal lymph nodes situated to the right of the spinal column as well as many on the left side and in the pelvis were replaced by soft friable pinkish white neoplastic tissue. Except for the tumor growth about the right kidney, all of the tumor was in lymph nodes or in bone, as will be described later. In some places, small hemorrhages had taken place in the neoplastic nodes. The tumor tissue was so soft that it crumbled easily and seemed to be almost devoid of stroma.

The bodies of the tenth thoracic and third lumbar vertebrae were practically destroyed by a friable infiltrating neoplasm which grew apparently from within the bone, involving first the bone marrow and extending peripherally to invade and erode the cortical portions of these bones. The sacrum just to the right of the midline was also destroyed and eroded by tumor tissue. In all these places the neoplastic tissue could be scooped out readily. It was grayish pink, soft, moist and often hemorrhagic and contained almost no detectable stroma.

Grossly, the nature of the neoplasm was difficult to determine. Multiple myeloma immediately suggested itself, especially since Bence Jones protein was said to have been found in the urine during life. However, multiple myeloma rarely metastasizes to viscera. Primary lymphoblastoma of the retroperitoneal lymph nodes with metastases to bone and to other organs was a likely possibility. Perhaps the tumor was an acute form of Hodgkin's disease. From gross examination alone we were inclined to favor the diagnosis of primary lymphoblastoma of the retroperitoneal lymph nodes, possibly acute Hodgkin's disease.

Microscopic Examination.—Heart: The muscle cells of the left ventricle of the heart were normal in size. Many of them were hydropic, and here and there were small vacuoles which apparently had contained fat. These degenerative changes were most pronounced in the subendocardial regions. Several small foci of necrosis of the myocardial cells also were found. In these regions the affected cells showed a loss of the normal striations and granulation of the cytoplasm with a tendency toward acidophilic staining. Endothelial leukocytes were present in the subendocardial regions. The epicardium and endocardium showed no noteworthy histologic changes.

Aorta: The aorta, especially in the abdominal portion, showed nothing of note histologically except moderate hypoplasia. The lumen of the vessel was slightly less than 1 cm. in diameter. In the adventitia of the vessel there was extensive local infiltration of a rapidly growing malignant tumor composed of small and large irregularly round or oval discrete undifferentiated cells, many of which were multinucleated. The growth did not affect the media or the intima of the vessel. The tumor was apparently an extension into the adventitia from adjacent retroperitoneal lymph nodes. The neoplasm will be described at more length.

Lungs: Sections from the right lung showed moderately edematous vesicular tissue. In one section a large metastatic neoplastic mass was present. Like that already described, this tumor consisted of great numbers of discrete round or oval cells, often multinucleated, with little stroma, and large numbers of thin-walled congested blood vessels were present in it and probably accounted for the absence

of foci of necrosis. Often the cells appeared to be confined in narrow, elongated spaces surrounded by thin delicate strands of connective tissue. Here and there slight hemorrhages had recently occurred. In these regions phagocytic endothelial leukocytes filled with blood pigment (hemosiderin) were present in considerable numbers. A single hyaline scar was observed in the tumor tissue. Adjacent to it a fairly large branch of a pulmonary artery was thrombosed, and



Fig. 12 (case 4).—The patient had secondary tumor in the lung. The photomicrograph shows a portion of the tumor that has completely destroyed the pulmonary parenchyma. Several multinucleated cells are shown.

the thrombus was undergoing organization. The scar appeared to be a small healing infarct.

In some sites the neoplastic cells infiltrated the pulmonary stroma rather widely, especially in the interlobar septums. In other places the growth was present with blood or lymph vessels. It was believed that the tumor reached the lung by means

of the blood and that further growth was by direct extension through tissue spaces or by way of the lymphatics.

Adjacent to the new growth the pulmonary tissues were edematous, and the alveoli contained many endothelial leukocytes, some of which were phagocytic. In some of the alveoli masses of fibrin also were present, but there was no evidence



Fig. 13 (case 4).—Several alveoli containing masses of monocytes and fibrin are shown. These alveoli are adjacent to a large mass of secondary neoplasm, and the cells in the alveoli are considered to be neoplastic. Multinucleated cells are shown.

of an infectious inflammatory process. The reaction was apparently secondary to the infiltration by the tumor of the pulmonary tissue.

A section from a lymph node in the region of the hilus of the right lung showed extensive infiltration by the same type of tumor as that in the right lung.

The neoplasm appeared definitely to be a metastasis and not a primary growth. The same histologic features which characterized the metastasis in the right lung were found in this tumor.

Sections from the left lung showed congested, slightly edematous vesicular tissue. In two of the sections recent typical hemorrhagic infarcts were present. At the lower edge of one of these, a large thrombosed branch of a pulmonary artery was observed. This was undoubtedly the cause of the infarct. In the infarcted regions, the pulmonary tissues were undergoing degeneration, and large numbers of red blood cells and much fibrin and serum were present in the alveoli. The edges of the infarcts were fairly sharp. The adjacent vesicular tissue was edematous; the more remote tissues showed no noteworthy changes. No neoplasm was found in the sections studied.

Spleen: The spleen was congested. Occasional areas in which slight hemorrhages into the pulp had taken place were observed. There was no histologic evidence of tumor metastasis in the sections studied.

Pancreas: In general, the acinar tissue in the pancreas was histologically normal and was well preserved. In several small foci the structural pattern of the pancreas was destroyed by the infiltration of a metastatic neoplasm which resembled the growths already described. The malignant cells infiltrated the inter-acinar stroma and compressed or destroyed the acini and islets of Langerhans which were in the affected region. The islands of Langerhans were abundant and appeared well preserved. Many of these structures were hypertrophied, being from two to four times the normal size. The island cells showed no abnormal changes.

Liver: The liver was the seat of marked fatty degeneration; practically all the parenchymal cells, especially those in the central portions of the lobules, contained small and large fat vacuoles. In some places, especially in the subcapsular regions, there was evidence of early acute necrosis of small groups of hepatic cells. In general these foci were in the peripheral portions of the lobules, and in practically all of the periportal spaces polymorphonuclear leukocytes were abundant. The liver was thus the seat of marked fatty degeneration as well as acute cholangitis with acute focal necrosis of parenchymal cells in the peripheral portions of the lobules. There was no evidence of metastatic neoplasm in the liver.

Adrenal Glands: The adrenal glands showed nothing of note histologically.

Kidneys: Sections from the kidneys showed two distinct types of lesions: first, typical small unencapsulated metastatic tumors similar to those described; second, acute inflammatory lesions which involved practically all of the convoluted tubules—early acute tubular nephritis. In general the glomeruli showed little of note aside from acute congestion. The convoluted tubules, however, as well as the renal stroma about them, were infiltrated with great numbers of polymorphonuclear leukocytes and occasional strands of fibrin. Fluid was not abundant. Often the leukocytes were in the process of removing necrotic tubular epithelial cells. Henle's loop and the collecting tubules were not inflamed, but in some of them small masses of purulent exudate, presumably from the convoluted tubules, were present. The lesion was considered to be acute tubular nephritis of toxic origin.

The tumor metastases were small, consisted of large accumulations of atypical cells similar to those found in other organs and completely destroyed the parenchyma of the kidney wherever they were present. The cells were separate and discrete, appeared round or oval with lobulated, irregular nuclei and had little stroma. Mitoses were frequently seen.

Genitalia: The myometrium and the endometrium showed nothing of note. The endocervix contained many large retention (nabothian) cysts but was otherwise not remarkable. The ovaries were normal. Sections from veins in the broad ligament showed them to be acutely thrombosed.

Retroperitoneal Lymph Nodes: Lymph nodes from about the aorta, as previously noted, as well as about the inferior vena cava and in other portions of the retro-

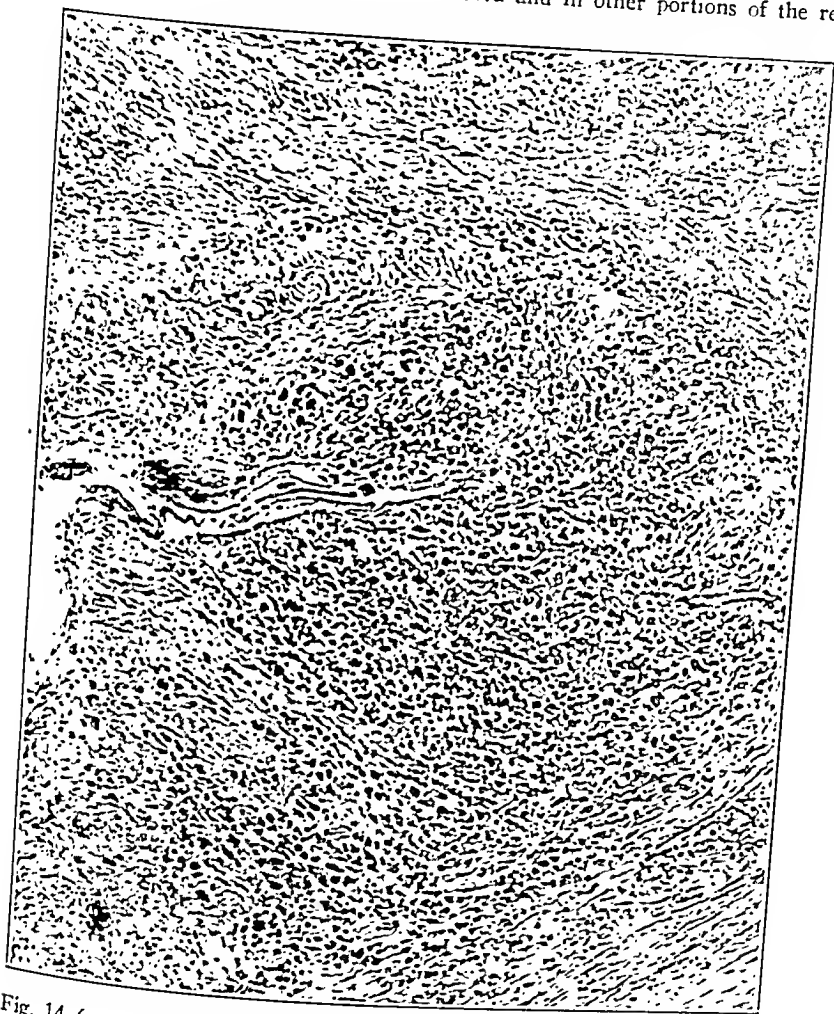


Fig. 14 (case 4).—Heavy infiltration of tumor cells into the periaortic tissues.

peritoneal tissues, were the seat of a rapidly growing highly invasive neoplasm. The cells varied considerably in size and shape, but tended to form no recognizable structures. They were undifferentiated and primitive. Mitotic figures were present in large numbers. The most typical cells were large and irregular and had deeply pigmented lobulated nuclei. Often the nuclei were multiple. These cells resembled somewhat megakaryocytes of the bone marrow. If this is true, the tumor may have been an acute form of Hodgkin's disease, although the tendency to fibrosis was slight.

However, other varieties of cells recalled primitive bone marrow cells and thus suggested myeloma of the myeloid type.

Sections from the vena cava showed that the tumor had penetrated the vessel wall from without and had led to the formation of a thrombus which completely filled the lumen.

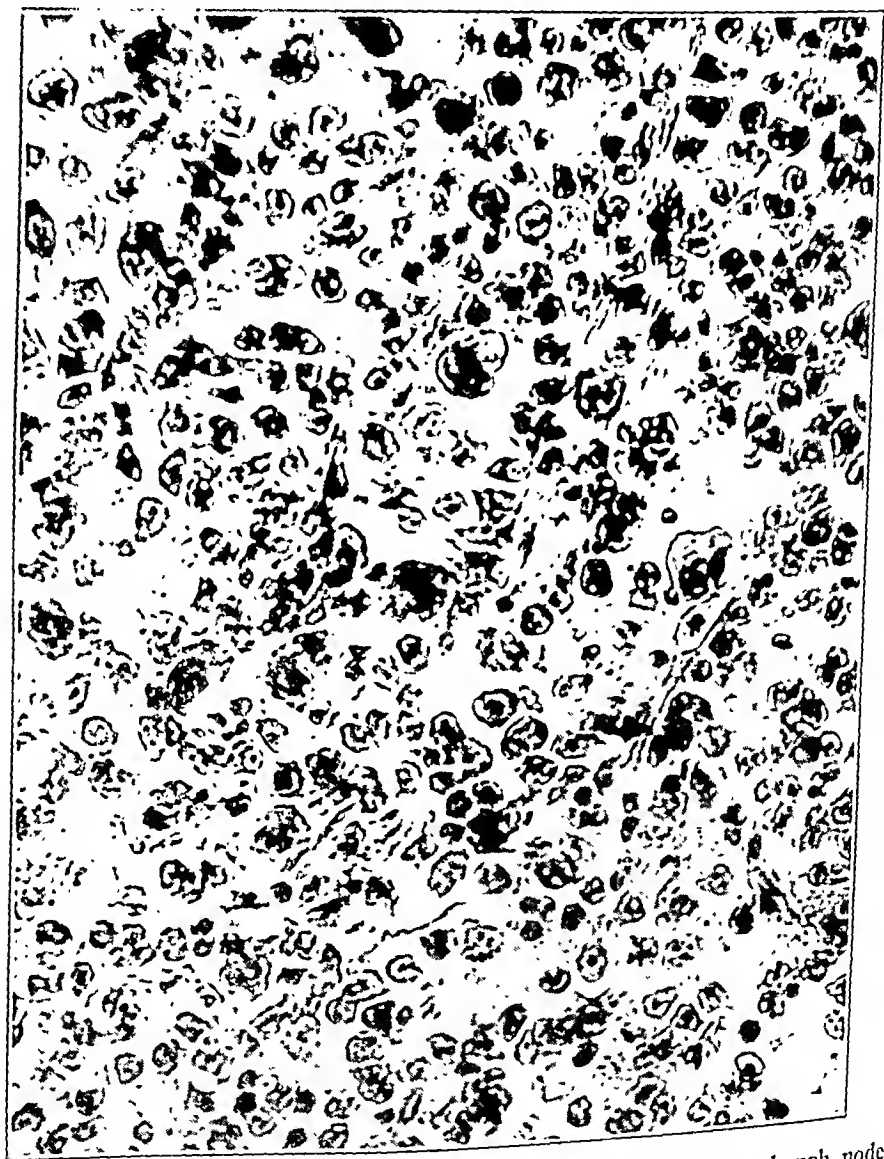


Fig. 15 (case 4).—Photomicrograph showing the structure of a lymph node replaced by tumor cells that vary in size and shape and do not tend to form recognizable structures. Many multinucleated cells are shown.

Bone Marrow: Sections from the marrow of the right side of the sacrum and from that of the bodies of the tenth dorsal and the third and fourth lumbar vertebrae all showed neoplasm of the same type as that already described. Foci of necrosis were present, but even though the fibrous stroma was fairly abundant, there were no large foci of sclerosis. The neoplastic cells, although they varied morphologically like those in the lymph node, appeared to be of bone marrow origin.

Summary.—In this case the anomaly consisted of a rapidly growing malignant tumor of the retroperitoneal lymph nodes and of the bone marrow of the sacrum and several vertebral bodies. Histologically the tumor was composed of highly undifferentiated cells believed to have their origin in the bone marrow. In our opinion, therefore, the neoplasm was multiple myeloma of the myeloid type.



Fig. 16 (case 4).—Photomicrograph of vertebral marrow. The marrow cells are largely replaced by tumor cells. Several multinuclear tumor cells are shown.

If Hodgkin's disease is considered a primary tumor of the bone marrow with the megakaryocyte as the cell of origin, it is not possible to exclude it as a possible diagnosis. Dr. E. M. Medlar of Mount McGregor, N. Y., expressed the belief that the tumor was characteristic of acute Hodgkin's disease. Dr. F. Parker Jr. of Boston said that he "felt pretty sure" that the diagnosis was acute Hodgkin's disease. Dr. F. B. Mallory of Boston did not wish to commit himself.

TABLE 9.—Data on the Patient in Case 5

Date	Was- ser- mann Tests	Blood Pres- sure, mm. of Mercury	Hemo- globin, per Cent	Blood Counts					Blood Chemistry					Additional Observations		
				Red Blood Cells	Color Index	White Blood Cells	Differential			Non- protein Nitrogen, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Icteric Index	Carbon Dioxide- Combining Power, Vol. per Cent			
							Poly- mor- pho- nu- clears	Lym- pho- cytes	Myelo- cytes						Un- deter- mined	
2/ 6/32	52	3,080,000	0.73	3,600	43	47	2	8	Urine contained casts
4/ 4/32	..	110/68	
4/10/32	..	110/70	
4/17/32	..	112/70	
6/22/32	..	100/40	
7/13/32	..	125/60	37	2,230,000	3,800	
8/ 3/32	..	110/60	38	2,450,000	
8/10/32	..	118/55	
8/14/32	..	140/60	
9/ 3/32	35	1,740,000	0.9	10,000	72	28	1	2	
9/ 4/32	
9/ 5/32	3.125	38	1.015	+	
9/ 7/32	—	105	
9/22/32	

Röntgen examination showed that the sella turcica was normal in size; the posterior cleft process was not well visualized.
Hence Jones protein was not present; urine contained many granular and hyaline casts.
Culture of the blood yielded no growth.
Culture of the blood yielded no growth.

Dr. James Ewing and Dr. Fred W. Stewart of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, felt that this was a case of myeloma of the myeloid series. They stated further that "it is difficult to assign an origin in these typical cases, that one can't feel sure the erythroblastic origin is out of the picture. The giant cells look like abortive megakaryocytes."

Despite what appeared to be real differences of opinion, therefore, the general opinion concerning the tumor was that it was of bone marrow origin, regardless of the name used in diagnosis. The neoplasm was definitely not primary in the lymph nodes, and the gross diagnosis of lymphoblastoma had to be set aside.

Anatomic Diagnoses.—The final diagnoses were: multiple myeloma of the myeloid type of the third and fourth lumbar and tenth thoracic vertebrae and of the sacrum with metastases to the retroperitoneal lymph nodes, the inferior vena cava, the pancreas, the kidneys and the right lung; marked erosion of the tenth thoracic and third and fourth lumbar vertebrae and of the sacrum; thrombosis of the inferior vena cava and of the iliac, uterine and pulmonary veins; hemorrhagic infarcts of the lungs; acute focal necrosis of the myocardium; acute bilateral nephritis of the tubules; stricture of the right ureter; right hydronephrosis; fatty degeneration of the heart and the liver; hypoplasia of the aorta.

CASE 5.—E. G., a 60 year old painter, was admitted to the Albany Hospital in moribund condition on Sept. 2, 1932. During the previous eighteen months he had been seen in the outpatient department a great many times and had been treated for a large variety of complaints, including chronic cough, weakness of the legs, dyspnea on exertion, blurring of vision and frontal headache. In February 1932 he had been admitted to the hospital because of increasing weakness, cough and brownish discoloration of the skin and the mucous membranes. At that time an excised portion of skin gave a negative reaction when tested for iron and showed the presence of melanin. After three weeks he was discharged with instructions to adhere to a high caloric diet and to rest as much as possible. A diagnosis of possible Addison's disease had been made. He was again followed in the outpatient department but was observed to be going gradually downhill. The weakness of the calves of his legs continued and grew more marked; at times he suffered epistaxis of considerable severity. Late in August his symptoms became much more marked; the headaches increased in severity and were accompanied by vomiting and dizziness. In the week before admission he became disoriented, and three days before entering the hospital he lapsed into a semicomatose state.

At the time of admission the patient was too weak to respond to questioning. There was marked bronzing of the skin, particularly of the face and the neck. The pupils reacted to light and in accommodation. The teeth were missing. The throat was somewhat injected. There were small pigmented areas on the hard palate. No enlarged lymph nodes were present. Examination of the heart revealed nothing unusual. The lungs were essentially clear. The abdomen and the extremities were not remarkable except for the pigmentation.

The patient never rallied from the semicomatose state. He was given dextrose intravenously. A blood transfusion was contemplated but not carried out because no satisfactory donors were available, the patient's serum agglutinating even his own cells. Two hours after admission he died.

Gross examination of the bone marrow at autopsy showed that the marrow of the ribs had been replaced by a white gelatinous friable material, the bulk of which was far greater than the normal bulk of the marrow content in these bones. The increased amount of this substance had apparently caused thinning of the bony cortex of the rib and had led to weakening of the structures. The ribs were

TABLE 10.—Summary

Case and Patient	Sex and Age	Presenting Symptom	Blood Pressure	Blood												Bence Jones Protein Examinations	
				Hemoglobin, per Cent		Red Cell Count, Millions *		White Cell Count		Differential Count †							
				Maximum	Minimum	Maximum	Minimum	Maximum	Minimum	Polymorphonuclear Leukocytes, per Cent		Lymphocytes, per Cent		Myelocytes, per Cent			
										Maximum	Minimum	Maximum	Minimum	Maximum	Minimum		
Case 1 D. A.	M 57	Pain in back, right side of chest and shoulders	See table 3	95	72	5.69	3.50	10,000	3,950	84	60	34	12	7.5	3	28	
Case 2 R. H.	M 44	Lump in right groin	See table 7	103	75	5.33	4.15	15,200	9,200	82	63	28	13	5	4	5	
Case 3 H. H.	F 62	Pain in lower part of the back	See table 8	101	63	5.07	3.20	10,020	4,800	68	62	35	20	10	2	3	
Case 4 N. D.	F 24	Pain in lower part of the back radiating about hips and abdomen	80/60	70	52	3.74	No other count	26,400	7,850	72	72	20	20	3	3	2	
Case 5 E. G.	M 60	Generalized "bone pain," sharpest in midportion of the back	See table 9	52	38	3.68	1.74	10,000	3,600	72	43	47	23	2	1	1	

* No nucleated red cells were noted in any of the cases.

† In none of the cases were the basophilic or eosinophilic counts abnormal.

‡ At no time was Bence Jones protein found, and depending on the biopsy alone, we made chemical examination. In respect it appears that it would have been better to perform the routine chemical examinations of the blood.

Tissue	Kidney Changes (Observed at Autopsy)	Locations of Bone Lesions (Ascertained by Roentgen Examination)	Locations of Extraskeletal Involvement	Spontaneous Fracture	Diagnoses
a trace of in; finely at casts half the occasionally to cast	A few small subcapsular scars consisting of dense fibrous tissue infiltrated by various numbers of lymphocytes. Renal tissues in gen- eral, glomeruli, vascular system and renal pelvis not unusual	Vertebrae, ribs, skull (including ramus of each mandible), clavicles, humeri, scapulas, radii, ulnas, femurs; generalized atrophic changes in bones of hands but no evidence of tumor	None	Present in rib	Primary diagnosis of hyperparathy- roidism after roent- gen examination; diagnosis changed after chemical examination and further roentgen study
Plant No. of album- in; most com- of patient that his had this for the years absence of yellow little to it; it; casts on large exami- the hospital	Capsules, normal thickness. Cortices, scattered foci of sclerosis with lymphocytic infiltration here and there. Glomerular capillaries, con- gested; many proliferated; many completely changed into masses of dense hyaline connective tissue; fibrosis of Bowman's capsule. Tu- bules, both postmortem and paren- chymatous degeneration of epithelial cells in both cortical and medullary portions; many cells desquamated and lying free in lumens; small hyaline casts in many collecting tubules. Connective tissue stroma throughout kidneys increased, loose and edematous. Large blood vessels, slightly thickened internal coats. The renal changes were those of mild chronic vascular nephritis	Pubic bone, skull and seventh rib	Prostate gland and peri- prostatic tis- sue (by direct invasion)	Present in pubic bone	Constant diagnosis of general carcin- omatosis, based on mass found in pelvis and on biopsy of tumor in fore- head which yielded diagnosis of meta- static epithelial tumor
exam- in; a trace in once; amount with a trace in; micro- scopic ways	Branches of renal artery, moderate degree of thickening. Glomeruli, occasionally hyalinized. Convoluted tubules, marked swelling, cloudiness and granularity of the epithelium; many of these cells without definite cell outlines; between some of the tubules, increased amount of fibrous tissue	Humerus, ribs, verte- brae, skull, femurs	Heart, spleen, liver (?), peri- ovarian tissue and peri- adrenal fat	Present in hu- merus and rib	Patient admitted three times; first diagnosis, flatfoot; second, possible metastatic carcin- oma; third (after finding Bence Jones protein), possible multiple myeloma
exam- in; a trace in once; in; obser- ways	Two types of lesions: (1) typical small unencapsulated metastatic tumors similar to those described elsewhere; (2) an acute inflammatory lesion involving all convoluted tu- bules—early acute tubular nephritis. The tumor metastases consisted of large accumulations of atypical cells similar to those formed in other organs, which completely destroyed parenchyma of kidneys wherever they were present. The cells were separate and discrete, appeared round or oval with lobulated irreg- ular nuclei and had little stroma. Mitoses were frequent	Vertebrae, sacrum and acetabulum	Lungs, peri- aortic tissue, retroperitoneal lymph glands, mediastinal lymph glands, pancreas, right kidney	Absent	Tentative diagnosis of possible myc- eloma or secondary carcinoma
exam- in; a trace in; obser- ways	Kidney essentially normal	No roentgenograms made	Heart and spleen	No roent- geno- grams made	Possible Addison's disease or secondary carcinoma

easily broken between the fingers. Examination of several ribs was convincing evidence that all of them were so affected.

The anatomic diagnosis was: cutaneous melanosis with old cerebral hemorrhage and questionable tumor of the bone marrow.

Microscopic Examination (Dr. Victor Jacobsen).—Heart: There was marked edema of epicardial fat. At the base of the left ventricle there was a coarse interstitial fibrosis with a few plasma cells and monocytes in the stroma. Muscle fibers showed hydrops and a normal amount of yellowish perinuclear pigment.

Spleen: In the spleen there was much hemosiderin both free and in phagocytes. Some phagocytes contained erythrocytes. Beneath the capsule was a zone in which there were many cells resembling somewhat the predominant cell in the vertebral and rib marrow.

Bone Marrow: The vertebral and the ilial marrow had been replaced by a cellular neoplasm. The type cell had some resemblance to the plasma cell but with variations; often it looked much like an erythroblast. Typical plasma cells were present in small numbers. Most of the cells were arranged in long narrow cords, separated by a delicate stroma, in which blood channels were inconspicuous. Invasion of the bone marrow by fat occurred. The bone cortex was thinned out, but there was no evidence of bone erosion or circumscribed marrow tumor. Mitoses were rare. The condition seemed to be a rare type of an essentially plasma cell tumor, a diffuse myelomatosis. The femoral marrow showed the picture of severe secondary anemia but with scattered cells of the same appearance as those in the vertebrae.

The microscopic diagnosis confirmed the diagnosis made after the gross examination. In addition, the following observations were made: subdural hemorrhage; chronic leptomeningitis; granular ependymitis; congenital asymmetry of the cerebrum; unilateral degeneration of the pyramidal tract; diffuse myelomatosis.

SUMMARY AND CONCLUSIONS

There were definite evidences of metastasis in 3 cases, including metastasis to the lung in 1 case.

There was widespread direct extension of the disease in case 2; in case 5, there was no evidence of metastasis or of direct extension.

In 3 of the 5 cases, Bence Jones protein was present in the urine.

The urinary findings were inconstant.

Roentgenograms must be examined skilfully.

In 4 of the 5 cases, pain in the back was the presenting symptom.

Though low blood pressure was present in 2 of our cases, it should not be considered as a pathognomonic sign.

Errors in diagnosis, as demonstrated by our cases, may sometimes be avoided by consistent determinations of the chemical composition of the blood.

All patients with pain in the back, especially those in the sixth decade of life, should be looked on with the idea that multiple myeloma may be present. This is especially true in those cases in which no injuries or only minor injuries appear in the history.

The cases reported are from the services of Drs. T. Ordway, A. W. Ehling and J. L. Donhauser.

PHYSIOLOGIC BEHAVIOR OF THE HUMAN APPENDIX AND THE PROBLEM OF APPENDICITIS

REACTION OF THE APPENDIX TO DRUGS

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MINNEAPOLIS

PART 1. INTRODUCTION

I. PURPOSE OF THIS STUDY

Although a host of theories as to the etiology of acute appendicitis has been offered, many with strong supporting evidence, the disease has not been proved capable of experimental production either in man or in related species except by the obstructive mechanism.¹

By longitudinal section of 91 surgically removed appendixes fixed in solution of formaldehyde, Wangenstein and Bowers² found all the gangrenous specimens to show obstruction of the lumen, but in only 72 per cent of 43 cases of acute suppurative appendicitis was obstruction demonstrable by this method, leaving 28 per cent of the group, or 12 cases, in which no obstruction could be demonstrated.

Through the studies reported in this paper it has been shown that a functional factor exists which may reasonably explain the absence of organic obstruction in some cases. Experiments will be outlined which have approached the nature of this functional factor from several angles and which enlarge on the application of the obstructive theory of the origin of appendicitis. The general plan of this paper is to record investigations on the following points:

1. The degree and nature of the muscular activity of surviving excised human appendixes, as determined by means of water bath studies.

From the Department of Surgery, University Hospitals.

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A condensation of a thesis submitted to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Surgery.

1. Wangenstein, O. H., and Dennis, C.: (a) Experimental Proof of the Obstructive Origin of Appendicitis in Man, *Ann. Surg.* **110**:629, 1939; (b) The Production of Acute Appendicitis (with Rupture) in Higher Apes by Luminal Obstruction, *Surg., Gynec. & Obst.* **70**:799, 1940.

2. Wangenstein, O. H., and Bowers, W. F.: An Experimental Study of the Obstructive Factor in the Genesis of Acute Appendicitis, *Tr. West. S. A.* **45**:195, 1935.

2. The muscular activity of the human appendix as seen in specimens in situ made available by appendicostomy.
3. The importance of the neuromuscular mechanism of the appendix, evaluated through the action of drugs.
4. The absolute resistance to outflow (of fluid through the appendix into the cecum) and its relation to disease of the appendix.
5. The role of neuromuscular activity in initiating acute appendicitis.
6. The relation of muscular activity to appendical pain and the effect of epinephrine on it.
7. The contribution of the obstructive theory in the etiology of appendicitis to the explanation of the cause of peritonitis in certain cases (data on seepage through the appendical wall).
8. The relation of increased intraluminal tension to rupture.
9. The relation of the observations on neuromuscular activity to the gross and microscopic pathologic observations.

II. SURVEY OF THE LITERATURE ON THE NATURE OF THE MOVEMENTS OF THE HUMAN APPENDIX

A. *Motility of the Excised Ileum*.—Although Haffter³ first discovered that excised intestine will continue to contract rhythmically, the bulk of the early work in this field was done by Magnus,⁴ who showed that with proper recording devices both layers of muscle could be shown to perform small regular "pendular" contractions with a period of five to seven seconds and also peristaltic or tonus waves of greater amplitude and with a period of twenty to one hundred seconds. The presence of dextrose or the absence of oxygen bubbling through Locke's solution which he used as a medium proved inhibitory to continued activity. Gunn and Underhill⁵ showed ten years later that these contractions are independent of any of the nerves of the intestine and therefore are myogenic in origin.

3. Haffter: Neue Versuche ueber den Nervus splanchnicus, Ztschr. f. rat. Med. **4**:322, 1854; cited by Magnus.^{4a}

4. Magnus, R.: (a) Versuche am überlebenden Dünndarm von Säugetieren: I. Mitteilung, Arch. f. d. ges. Physiol. **102**:123, 1904; (b) II. Mitteilung. Die Beziehungen des Darmnervensystems zur automatischen Darmbewegung, *ibid.* **102**:349, 1904; (c) III. Mitteilung. Die Erregungsleitung, *ibid.* **103**:515, 1904. (d) IV. Mitteilung. Rhythmizität und refraktäre Periode, *ibid.* **103**:525, 1904. (e) V. Mitteilung. Wirkungsweise und Angriffspunkt einiger Gifte am Katzen-darm, *ibid.* **108**:1, 1905.

5. Gunn, S. H., and Underhill, S. W. F.: Experiments on Surviving Mammalian Intestine, Quart. J. Physiol. **8**:275, 1914.

Alvarez and several co-workers⁶ found that best rhythmic movements in the water bath could be obtained if the specimen were chilled in Locke's solution for a few hours before the study and also that if the muscle is to survive abundant oxygen must be supplied for the specimen or metabolism must be checked by refrigeration. He emphasized the myogenic nature of the rhythmic contractions seen in the intestine and championed the theory that gradients of various manifestations of physiologic activity, such as the rate of spontaneous rhythmic contractions, the rate of oxygen usage, the rate of carbon dioxide output and the lactic acid content of the resting muscle, determine the movements of the intact bowel. In any excised segment of small bowel, for instance, he found the cephalad portion to have the fastest rate of rhythmic contraction and therefore to determine the rate of contraction of the entire segment and the direction of propulsion of the contents, just as the area of fastest rhythmicity in the heart, the sinoatrial node, sets the pace for the whole organ.

B. Motility Studies on the Surviving Excised Human Appendix.—The surviving excised human appendix has been studied in similar fashion by a number of workers,⁷ most of whom used Magnus' methods

6. (a) Alvarez, W. C.: Differences in the Action of Drugs on Different Parts of the Bowel, *J. Pharmacol. & Exper. Therap.* **12**:171, 1918; (b) Physiological Studies on the Motor Activities of the Stomach and Bowel in Man, *Am. J. Physiol.* **88**:650, 1929; (c) The Mechanics of the Digestive Tract, ed. 2, New York, Paul B. Hoeber, 1919. (d) Alvarez, W. C., and Hosoi, K.: The Latent Period of Intestinal Muscle, *Am. J. Physiol.* **89**:201, 1929. (e) Alvarez, W. C., and Mahoney, L. J.: The Myogenic Nature of the Rhythmic Contractions of the Intestine, *ibid.* **49**:421, 1922. (f) Asciano, H., and Alvarez, W. C.: Factors That Influence the Conservation of Intestinal Rhythmicity After Death, *Am. J. Physiol.* **90**:611, 1929.

7. (a) Aschoff, L., and Pokorny, O.: Ueber die Beweglichkeit des Wurmfortsatzes, *Deutsche Ztschr. f. Chir.* **203**:175, 1927. (b) Cross, D. G. T. K.: The Action of Physostigmine (Eserine) and Pituitrin, *Brit. M. J.* **1**:9, 1924. (c) Gunn, J. A., and Whitelocke, R. H. A.: Observations on the Movements of the Isolated Human Vermiform Appendix, *Brit. J. Surg.* **2**:92, 1914. (d) Hara, S., and Uehara, T.: Pharmakologic über den ausgeschnittenen Wurmfortsatz des Menschen, *Jap. J. M. Sc., IV, Pharmacol.* **10**:130, 1937. (e) Holm, K.: Untersuchungen am ueberlebenden menschlichen Wurmfortsatz, *Arch. f. d. ges. Physiol.* **197**:411, 1922. (f) Miller, J., and Mann, J.: The Muscular Movements of the Appendix and Their Relation to Appendicitis, *Tr. Roy. Soc. Canada (Sect. V)* **22**:311, 1928. (g) Ricker, G.: Pathologic als Naturwissenschaft, Berlin, Julius Springer, 1924; cited by McCloskey.^{27c} (h) Rössle, R.: Die Beweglichkeit des Wurmfortsatzes, *Beitr. z. path. Anat. u. z. allg. Path.* **77**:121, 1927. (i) Ruf, S.: Die Appendicitis im Lichte der Ricker'schen Gefässnerventheorie, *ibid.* **75**:135, 1926. (j) Ulrich, L.: Ueber die motorischen Funktionen der Appendix, *Deutsche Ztschr. f. Chir.* **212**:119, 1928.

and recorded contractions of the longitudinal muscle by means of a muscle lever. Ruf⁷¹ and Aschoff and Pokorny⁷² maintained that the movements of the appendix are too feeble to prevent the stasis which Aschoff⁸ considered essential to the development of appendicitis. Ricker⁷³ thought that there were movements fully as active as those of the ileum, but most workers have been inclined to favor a middle stand. Ulrich,⁷⁴ the only one who has studied the activity of the circular muscle, attached a writing lever by a thread to the serosa opposite an anchored point; by the use of several of these, he tried unsuccessfully to demonstrate peristaltic activity in his specimens.

C. Motility Studies on the Human Appendix Through the Medium of Roentgenology.—A considerable number of roentgenologists have tried to elucidate the problem of appendiceal movements by means of the visualization which is frequently obtainable in the course of gastrointestinal roentgen ray studies.⁹ It is the consensus that active movement takes place and that filling and emptying occur in the presence of a filled cecum. Westphal and Schmidlein administered large (10 mg.) doses of pilocarpine intravenously during observation, and they reported spasm of the proximal portion, or "antrum," of the appendix. Wildegans, using roentgenocinematography, described definite peristaltic movements commencing at the tip and moving proximally.

D. Pharmacologic Studies of the Neuromuscular Mechanism of the Human Appendix.—1. Barium Chloride: Magnus^{4e} observed the stimulating action of barium chloride in small concentrations (1:10,000) on both the rhythmic contractions and the tonus of excised pieces of cat intestine. Various workers have confirmed this finding both for the ileum and for the human appendix in the water bath.¹⁰ Alvarez has shown that electrical variations occur in the muscle when contractions have not yet appeared and likened the barium in effect to a "clutch" connecting the muscle to an idling motor.^{6c}

8. Aschoff, L.: *Appendicitis: Its Etiology and Pathogenesis*, London, Constable & Co., 1931.

9. (a) Cohn, M.: *Die Appendix im Röntgenbilde*, Berl. klin. Wchnschr. **50**:326, 1913. (b) Hubeny, M. J.: *The Appendix with Especial Reference to Peristalsis*, Am. J. Roentgenol. **5**:293, 1918. (c) Schmidlein, E.: *Ueber die aktive Beweglichkeit und den Entleerungsmechanismus des Wurmfortsatzes*, Fortschr. a. d. Geb. d. Röntgenstrahlen **44**:141, 1931. (d) Westphal, K.: *Bewegungsmechanismus, Resorption und Pathologie des Wurmfortsatzes*, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **42**:99, 1930. (e) Wildegans, H.: *Medizinische Kinemato- und Photographie: VII. Die Bewegungen des Dickdarms einschliesslich des Wurmfortsatzes im röntgenkinematographischen Bilde*, Deutsche med. Wchnschr. **58**:1569, 1932.

10. Alvarez.^{6c} Gunn and Underhill.⁵ Hara and Uehara.^{7d} Holm.^{7e}

2. Epinephrine: Magnus^{4e} showed a diminution in tone and a temporary abolition of movements in cat intestine by the addition of epinephrine hydrochloride to a concentration of 1:20,000,000, and Gunn and Whitelocke^{7c} showed a similar effect with higher concentrations (1:250,000) in the human appendix. Hara and Uehara^{7d} observed a stimulating action of epinephrine if added in sufficiently low concentration.

3. Ephedrine: No mention has been found in the literature on the action of ephedrine on the appendical musculature.

4. Amphetamine: Myerson and Ritvo¹¹ and Beyer¹² agreed that amphetamine (benzedrine) sulfate administered orally causes relaxation of spasm throughout the alimentary tract, but Beyer described a brief preliminary increase in tone and rate of rhythmic contraction occurring before the inhibitory effect.

5. Acetylcholine: Starling¹³ stated that acetylcholine causes contraction of the intestinal musculature, but Puestow,¹⁴ on the basis of observations on a patient with cecostomy and eversion of the posterior cecal wall with inclusion of loops of small intestine, reported that acetylcholine caused increased activity in the small bowel and decreased activity in the colon. No reports have been found relating to its effect on the appendix.

6. Physostigmine: In his patient Puestow¹⁴ found the reaction to physostigmine to be similar to that to acetylcholine. Hara and Uehara^{7d} reported increased tonus and activity in the surviving human appendix.

7. Pilocarpine: Magnus^{4e} was much impressed by the rise in tone and increase in rate of rhythmic contractions of the intestine caused by the addition of 2 to 30 mg. of pilocarpine to a bath of 200 cc. of Ringer's solution. The effect has been corroborated for the bowel⁵ and for the appendix in the water bath.¹⁵ Marked contraction of the appendix in response to the drug has been observed directly by laparoscopy¹⁶ and also on roentgenologic examination (Schmidtlein^{9c} and Westphal^{9d}).

11. Myerson, A., and Ritvo, M.: Benzedrine Sulfate and Its Value in Spasm of the Gastro-Intestinal Tract, *J. A. M. A.* **107**:24 (July 4) 1936.

12. Beyer, K. H.: Gastric Emptying as Influenced by Benzedrine Sulfate, *Am. J. Physiol.* **123**:16, 1938.

13. Starling, E. H.: *Principles of Human Physiology*, ed. 7, Philadelphia, Lea & Febiger, 1936.

14. Puestow, C. B.: The Action of Drugs on Intestinal Motility. *Am. J. Physiol.* **123**:165, 1938.

15. Gunn and Whitelocke.^{7c} Hara and Uehara.^{7d} Miller and Mann.^{7f}

16. Kalk, H.: Eine Beobachtung über die Bewegungsvorgänge an der Appendix, *Deutsche med. Wchnschr.* **63**:772, 1937.

8. Atropine: There is unanimity of opinion among investigators that atropine abolishes the stimulating action of physostigmine, pilocarpine and acetylcholine¹⁷ in the appendix, as well as in other parts of the bowel. Magnus^{4e} found also that small doses of atropine sulfate (1:2,000) without previous medication caused stimulation of pieces of cat ileum and made the rhythmic contractions more regular. Solutions as concentrated as 1:1,000 made rhythmic movements at first more regular and then weaker, with complete cessation when the concentration was increased to 1:300. Holm^{7e} and Hara and Uehara^{7d} failed to find the stimulating action on surviving human appendixes.

9. Nicotine: Magnus^{4e} observed that a 1:4,000 concentration of nicotine stopped rhythmic movements of the intestine for a few minutes, after which the movements were resumed in the continued presence of the drug; a gradual increase in tonus also occurred over a period of half an hour. No reports have been found on the effect on the appendix.

10. Morphine: In his patient, previously described, Puestow¹⁴ observed increased activity in the small bowel and decreased activity in the colon after morphine had been given. Dvorak and his associates¹⁸ found morphine to increase the intestinal tone and peristaltic activity of the obstructed small intestine of the dog. Krueger¹⁹ summarized the literature on the effect of morphine on the intestinal tract and mentioned increased tone and increased peristaltic activity, though with decreased amplitude and no change in pendular movements in the large bowel; in the small intestine, on the other hand, morphine was reported to cause an increase in tone, in amplitude and in frequency of movements but a diminution in propulsive activity. Hara and Uehara^{7d} stated that the effect on the appendix varied with the dose but that increased activity could be obtained.

11. Papaverine: Hara and Uehara^{7d} observed obliteration of the barium effect and diminution of tone by addition of papaverine to the bath.

PART 2. EXPERIMENTAL PROCEDURES AND OBSERVATIONS

III. MATERIALS USED IN THIS STUDY

Observations were made on 272 excised appendixes. Two hundred and twenty-seven of these came from the operating rooms of the

17. Magnus.^{4e} Gunn and Underhill.⁵ Gunn and Whitelocke.^{7c} Hara and Uehara.^{7d} Holm.^{7e} Cohn.^{9a} Schmidtlein.^{9c} Westphal.^{9d} Kalk.¹⁶

18. Dvorak, H. S.; Carlson, H. A.; Erickson, T. C.; Smith, V. D., and Wangenstein, O. H.: Influence of Morphine on Intestinal Activity in Experimental Obstruction, *Proc. Soc. Exper. Biol. & Med.* 28:434, 1931.

19. Krueger, H.: The Action of Morphine on the Digestive Tract, *Physiol. Rev.* 17:618, 1937.

University Hospitals, 16 from the Minneapolis General Hospital²⁰ and 18 from the morgue of the University Hospitals. In 66 instances observations were made in the operating room. Eleven additional appendixes were studied in situ by means of appendicostomy with delayed opening. Three ureters also became available for study, 1 after excision and 2 while still in the patient.

At the University Hospitals appendicitis is treated by conservative measures if the history, signs and symptoms suggest that frank rupture has occurred.²¹ These measures include duodenal siphonage through an inlying nasal catheter, abdominal hot packs and oral administration of fluids. Six to eight weeks later the appendix is removed. An appendix obtained at such an appendectomy after an interval is called an "interval specimen." It was thus possible to study many appendixes for late effects of acute inflammation, as well as normal and acutely inflamed specimens.

IV. WATER BATH STUDIES TO INVESTIGATE THE DEGREE AND NATURE OF MUSCULAR ACTIVITY OF SURVIVING HUMAN APPENDIXES

A. *Apparatus*.—As emphasis has been placed on the resistance to flow of fluid through the lumen of the appendix by correlation with the clinical diagnosis²² and by production of appendicitis by ligature obstruction,¹ variations in resistance to flow have been recorded rather than the contractions of the circular muscle.

As illustrated diagrammatically in figure 1, the bath used in experiments for this purpose consisted of a horizontal tray containing 180 cc. of fluid, kept at 37 C. by a thermostat. At one end of the tray a glass cannula was fixed in position below the level of the fluid in the bath. A tube connected this cannula to an elevated flask of Locke's solution without dextrose fitted with an adjusting valve and a gravity drip bulb and to a recording mercury manometer. A pulley was mounted at the far end of the bath in order that a thread attached to the end of the specimen opposite the cannula might be led to a recording lever. An oxygen jet was fixed in one corner of the bath, and the fluid coming to the cannula was preheated to the temperature of the bath in a submerged coil of tubing, not shown in the diagram.

20. The surgical staffs of the University Hospitals and of the Minneapolis General Hospital assisted in the execution of this study.

21. (a) Adams, J. M., and Bancroft, P. M.: The Conservative Management of Appendiceal Peritonitis in Children, *J. Pediat.* **12**:298, 1938. (b) Ochsner, A.: Conservative Treatment of Appendical Peritonitis, New Orleans M. & S. J. **87**:32, 1934.

22. Wagensteen, O. H.; Buirge, R. E.; Dennis, C., and Ritchie, W. P.: Studies in the Etiology of Acute Appendicitis: The Significance of the Structure and Function of the Vermiform Appendix in the Genesis of Appendicitis: a Preliminary Report, *Ann. Surg.* **106**:910, 1937.

By virtue of the arrangement of the apparatus, the record obtained indicated the resistance to flow of fluid through the lumen and the variations in length of the specimen.

B. Procedure.—The freshly excised appendix was wrapped in gauze soaked in saline solution and placed in an ice box at a temperature of 2 to 7 C. After a few hours or days the specimen was transferred to the bath, which had been filled with Locke's solution without dextrose at the same low temperature. The tip of the appendix was amputated, and the distal end of the remaining specimen was slipped over the

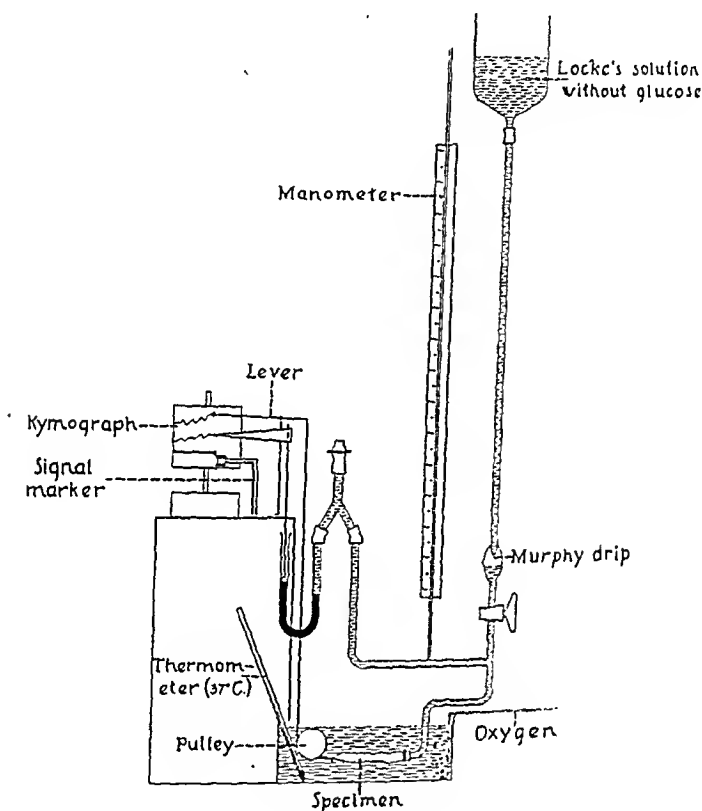


Fig. 1.—Schematic drawing of the apparatus used for water bath studies of surviving excised human appendixes.

cannula of the bath and securely tied. A thread was passed through one wall of the proximal end of the appendix, passed around the pulley, and led vertically up to the writing lever. A kymograph fitted with smoked paper for recording was approximated to the writing point of the lever and the mercury manometer. The flow of oxygen was started at once, and the temperature was gradually raised, reaching 37 C. in from thirty to forty minutes as a rule. The rate of flow through the lumen was usually 20 to 60 drops per minute, excess fluid leaving the bath by an overflow drain.

In all kymographic tracings shown, pressures are recorded in centimeters of water, and each rise of 20 cm. above the standard line indicates a 2 mm. shortening of the specimen.

C. Observations.—Most appendixes presented active rhythmic contractions both of the longitudinal muscle and of the circular muscle, those of the latter reflected by variations in pressure. As the temperature was raised, marked diminution and then a gain in tonus occurred, the latter appearing near body temperature and usually in association with the appearance of slow, large rhythmic contractions of both layers

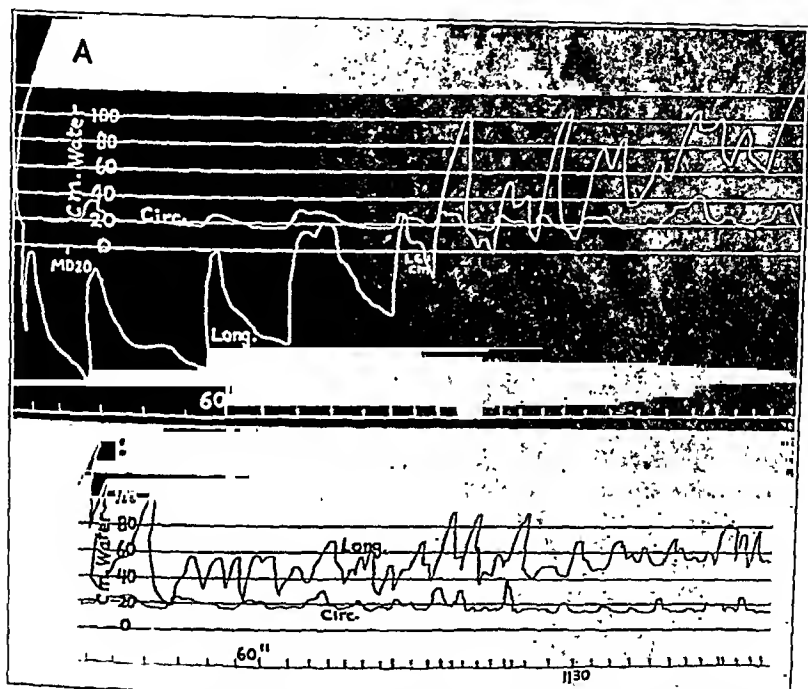


Fig. 2.—Kymographic records of the contractions of a surviving excised human appendix. *A*, early contractions; *circ.* indicates resistance to flow of fluid through the lumen (activity of the circular muscle), and *long.* indicates activity of the longitudinal muscle. The waves are large and slow, and an increase in tone is shown in the longitudinal layer. *B*, contractions during the second hour in the water bath. Changes in tonus are no longer marked, and the waves are more regular.

of muscle (fig. 2 *A*). After thirty to sixty minutes of movements, the changes in tonus became minimal and the waves faster and more regular, with an interval of ten to forty seconds (fig. 2 *B*). The fine pendular waves with a period of three to ten seconds described by Gunn and Whitelocke^{7c} were only occasionally seen in the water bath (though they were usually present in appendicostomy tracings). The rhythmic

contractions in the two muscle layers were usually but not necessarily synchronous, either layer occasionally presenting waves with no change in the other. An hour or two after the start of distinct waves a final loss of tone began gradually to occur, and the waves became smaller in amplitude, more irregular and usually faster, finally ceasing altogether.

D. *Influence of Inflammation on the Motility of Excised Appendices.*—Of all the previous investigators, only Ulrich⁷³ and Hara and Uehara⁷⁴ observed poorer contractions in inflamed specimens, and some made a point of stressing the lack of influence of inflammation (Gunn and White-locke⁷⁵ and Rössle⁷⁶). The behavior of specimens showing varying degrees of involvement is indicated in table 1, which shows that the degree of inflammation plays a decisive role in preventing subsequent development of activity. That the interference with movement is not a variation from person to person, with incidental inflammation, is

TABLE 1.—*The Effect of Acute Inflammation on the Occurrence of Spontaneous Rhythmic Contractions of Excised Human Appendices in the Study Bath*

	Number of Specimens			Per Cent of Specimens Showing Rhythmic Activity
	Strong Rhythmic Contractions	Weak Rhythmic Contractions	No Activity	
Appendices showing no microscopic evidence of inflammation	21	8	3	91
Acutely inflamed appendices.....	31	16	16	75
Gangrenous appendices	0	2	7	21
Total.....	52	26	26	71

indicated by two specimens a half of each of which was gangrenous and failed to show rhythmic movements, the other half showing less marked change and presenting active contractions.

E. *Influence of Chilling the Specimen on the Appearance of Motility.*—Gunn and Underhill⁷⁷ and Asciano and Alvarez⁷⁸ found that they were more successful in water bath experiments if the specimen was cooled before use. An attempt was made to assay the importance of this factor in the present study. Seven specimens were transferred directly from patient to study bath. In contrast to the observations in table 1, no waves appeared in 4 specimens, very poor ones in 2, and good ones in only 1.

Faradic stimulation was utilized on several specimens and particularly caused elevation in resistance to outflow, with a latent period one to four seconds, but in a chilled specimen no effect was observed. The maximal stimulus obtainable with two dry cells and a Helmholtz inductorium, so much had the irritability of the appendix been depressed. It was concluded, therefore, that chilling the specimen permitted relaxation of the appendix and adjustment of the apparatus without stimulation of the appendical musculature.

V. CONFIRMATION OF NEUROMUSCULAR ACTIVITY OF THE
HUMAN APPENDIX BY STUDY OF SPECIMENS IN SITU
MADE AVAILABLE BY APPENDICOSTOMY

A. *Procedure*.—Ten patients presenting cancer of the large bowel and 1 presenting ulcerative colitis were subjected to laparotomy for diversion of the fecal stream; at the time of this operation the appendix was incidentally delivered through a stab wound in the right lower abdominal quadrant sufficiently large to preclude compression of appendix or mesentery. After five or six days the tip was amputated and a no. 8 French soft catheter with the end cut off squarely was tied into the lumen.²² The resistance to the passage of fluid through the appendix into the cecum was determined continuously by an arrangement of flask, tubing and manometers similar to that previously described for the water bath experiments. The rate of flow was usually adjusted at 15 to 20 drops per minute.

B. *Observations*.—1. In the Fasting State: In fasting patients three types of waves were discernible. Pendular contractions with a period of seven to ten seconds and an amplitude of 2 to 5 cm. of water pressure were superimposed on what will be termed "small tonus waves," coming every thirty to ninety seconds and having an amplitude of as much as 20 cm. of water at times (fig. 3A). For the third type there were what will be termed "large tonus waves," or periods of increased activity, coming every ten to twenty minutes. Between these active periods only the pendular and smaller tonus waves were in evidence, and the resistance to flow at these times, the "basal level," usually hovered somewhere between 15 and 30 cm. of water. As an active period approached, the mean level rose gradually to a pressure 20 to 30 cm. above the basal level, and the size of the individual small tonus waves also increased.

The tracings under these circumstances, therefore, differed from the tracings of resistance to flow in the water bath chiefly in the higher basal level (usually 15 to 30 cm., as against 8 to 10 cm. in the bath) and in the presence of large tonus waves. It is because of the presence of the latter waves that the term neuromuscular rather than muscular is used, for these waves imply more than the rhythmic myogenic contractions seen in the water bath. An increase in the rate of flow of fluid was found to elevate the observed resistance to flow very little. In 1 case the basal level was between 20 and 25 cm. of pressure at 30 drops per minute but well above 30 cm. at 100 drops.

2. Comparison of Appendical Resistance to Outflow with the Intracecal Pressure: As has been previously reported,²² the resistance to flow in an appendix in situ made available by appendicostomy is not

due to the intracecal pressure, for if the catheter is slipped through the appendix and into the cecum, the resistance drops to 2 to 3 cm. of water pressure.

In the patient with ulcerative colitis, a terminal ileostomy was made in addition to an appendicostomy, and it was possible to insert a catheter into the lower segment of ileum, through the ileocecal sphincter and into the cecum, permitting simultaneous recordings of intra-appendical and intracecal pressures. In the vast bulk of the records made over a period of four days the two curves were roughly parallel, with the cecal

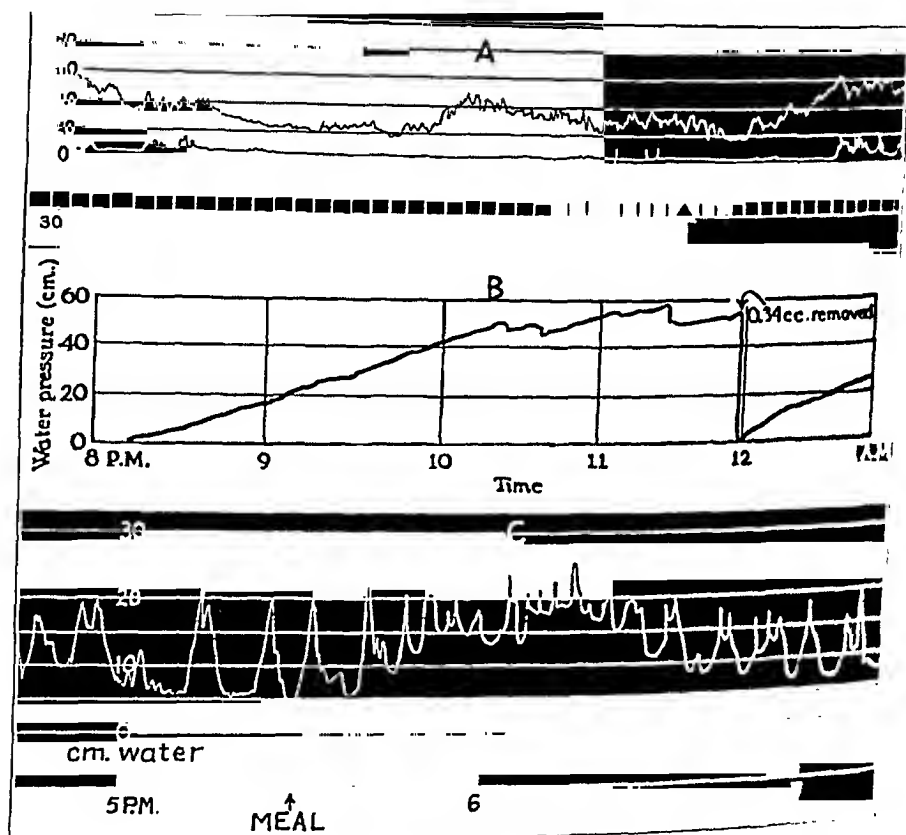


Fig. 3.—*A*, kymograph record of variations in resistance to outflow of appendix made available by appendicostomy (upper curve). Pendular waves, tonus waves and large tonus waves may be seen. The relative level of resistance and activity (obtained by insertion of a catheter through a terminal ileostomy opening, through the ileocecal valve and into the cecum) are indicated in the lower curve. The stimulating effect of subcutaneous injection of 12 mg. of morphine sulfate (arrow) is also shown; this effect was not obtained in the other two trials. *B*, pressure tracing made with a catheter in a specimen of appendix made available by appendicostomy (Wangensteen, Buirge, Dennis and Blodgett). A spontaneous rise in pressure from atmospheric to more than 50 cm. of water in three hours is shown. The lumen of the appendix was patent. The small, frequent and repeated rises at the top of the curve are considered due to a failure of continued secretion and rhythmic variations in resistance to outflow. *C*, a kymographic record showing the effect of the ingestion of food on the resistance to outflow in an appendicostomy specimen.

tracing about 20 cm. below the appendical; but on a few occasions the intracecal pressure was observed to rise above the level of the appendical resistance, particularly if the flow of fluid was stopped, an observation which may help to clarify the roentgenologic observation of filling of the appendix.

3. Proof That the Absolute Resistance to Outflow Is the Pressure Actually Present in the Appendix: It has been shown^{1a} that the normal mucosa of the human appendix secretes fluid at the rate of from 2 to 3 cc. per day. This constant flow of fluid, slow though it is, coupled with the previously demonstrated resistance to outflow would suggest that the very small amount of fluid normally present in the lumen of the appendix is under tension.

In order to test whether this actually is the case, a small volume manometer (requiring 0.62 cc. to raise the reading from 0 to 100 cm. of water) was connected by a closed system to the tip of an unobstructed appendix made available by appendicostomy. The fluid secreted by the organ elevated the pressure consistently, on one occasion to over 50 cm. of water in less than three hours (fig. 3 B). At about 50 cm. of pressure a sudden drop of 3 to 4 cm. occurred, only to be followed by a rise and then another drop, etc. This type of curve is interpreted as due to a balance between fluid secretion and the resistance to outflow varied by rhythmic contractions in the circular muscle. It follows that the intraluminal tension normally must be the level of the resistance to outflow.

4. Effect of the Ingestion of Food on the Resistance to Outflow in the Appendix in Situ Made Available by Appendicostomy: The type of fasting curve just described was altered to a considerable extent by the ingestion of food. The basal level rose 10 to 15 cm. as if the periods of increased activity had become merged, and this greater activity persisted for about two hours before again settling to the fasting level (fig. 3 C). In 1 instance simultaneous cecal readings were possible; the intracecal pressure rose only 6 to 8 cm. but might have risen higher had the flow of chyme from the ileum not been interrupted by ileostomy.

VI. EVALUATION THROUGH DRUG ACTION OF THE IMPORTANCE OF THE NEUROMUSCULAR MECHANISM OF THE APPENDIX

A. *Procedures.*—1. Water Bath Experiments: In attempting to evaluate the action of drugs on appendixes in the water bath, rhythmic contractions were allowed to develop until they had become fairly uniform. The agent was then added to the solution at a corner of the chamber as far from the specimen as possible. Unless otherwise indicated, the drug was added in aqueous solution and only one drug was used on each specimen.

Many of the specimens used were found on subsequent microscopic examination to be acutely inflamed. With each drug (with the exception of acetylcholine) experiments were performed until comparison of the effects in inflamed and in uninflamed appendixes could be made. No alteration of drug effect by any degree of inflammation was found, provided only that spontaneous movements appear before administration of the drug.

2. Appendicostomy Experiments: In assaying the effects of drugs on appendixes in situ made available by appendicostomy, the subcutaneous route of administration was usually followed. The drug was not given until three hours after the last meal, and administration was regularly preceded by a one hour control recording.

B. *Effect of Drugs on the Neuromuscular Activity of the Appendix.*
—1. Barium Chloride: In many instances in which appendixes were being studied in the bath it was found that the addition of 30 to 50 mg. of barium chloride crystals hastened the initiation of contractions, and in some cases it seemed probable that deterioration would have occurred without manifestation of contractions at all had the drug not been added. It was used in about half the experiments (fig. 4 A). The effect of previous addition of this quantity of barium chloride to the bath on the responses to the drugs used was carefully checked for all the drugs tested except acetylcholine, and only in the case of amphetamine was any difference encountered.

2. Epinephrine: In 1 instance a concentration of 1:900,000 of epinephrine caused a very slight increase in amplitude of tonus waves in the water bath; this, however, was the only change suggesting stimulation, for the rate of contraction was slowed slightly and the pendular contractions, which had been evident before the medication, disappeared afterward (fig. 4 B). In 8 other cases larger concentrations (up to 1:90,000) caused a loss of tone in both layers of muscle, reducing the size of the waves in 1 instance and abolishing them altogether in the remainder (fig. 4 C).

Epinephrine hydrochloride (1:1,000 solution) was given subcutaneously in 0.67 cc. doses to each of 3 patients with appendicostomies. In all cases a distinct quieting effect was apparent. In 1 case all the great and small tonus waves were eliminated for nearly an hour and the mean level of pressure was lowered 5 cm. of water; in the others, although the general pressure rose somewhat when the next period of activity was to be expected, the rise was less marked than in active periods before the medication, and the smaller tonus and pendular waves were nearly lost (fig. 4 D).

3. Ephedrine: In the water bath ephedrine sulfate was tested in thirteen experiments on 10 specimens in concentrations varying from 1:3,600 to 1:1,500, and the effect varied widely under similar circum-

stances, regardless of the degree of inflammation and regardless of the presence or absence of barium chloride. The commonest effect was a decrease in amplitude with an increase in rate of rhythmic contractions in both layers of muscle without definite change in tonus. In 4 instances the drug caused complete loss of rhythmic contractions.

The subcutaneous injection of 45 mg. of ephedrine sulfate in 2 cases in which appendicostomy had been performed eliminated the small tonus waves and weakened the pendular waves, abolishing them in 1 case. The effect lasted about forty minutes.

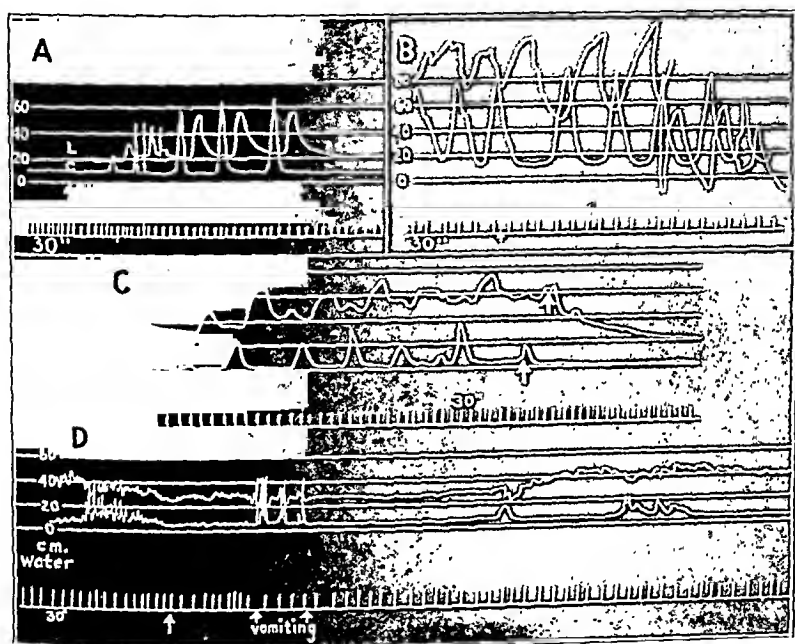


Fig. 4.—Kymographic records showing: (A) the efficacy of barium chloride, 1:4,000 (arrow at the left), in initiating rhythmic contractions in an excised appendix in the water bath and the abolition of the effect of the barium by papaverine, 1:11,000 (arrow at the right). B, slight increase in the amplitude of contraction obtained in the water bath on the addition of epinephrine to a concentration of 1:900,000 (arrow). The rate of contraction was slowed somewhat, and the pendular waves were abolished. Near the end of the record a correction was made to keep the pointer from rising over the top of the drum. This is the only instance in which any semblance of stimulation was obtained from epinephrine. C, the usual response of the surviving excised appendix to epinephrine hydrochloride, 1:180,000 (arrow). D, the effect of the subcutaneous injection of 0.67 cc. of epinephrine hydrochloride 1:1,000 on the resistance to flow of fluid at 20 drops per minute through the lumen of an appendicostomy specimen into the cecum (above) and on the intracecal pressure (below). The marked excursions of the cecal pressure shortly after the medication were due to vomiting. Loss of pendular waves in both the cecum and the appendix occurred, and the appendical resistance rose less high during the large tonus wave after the administration of epinephrine than before.

4. Amphetamine: Amphetamine sulfate²³ was tested in seventeen water bath experiments on 10 specimens, including a piece of rabbit ileum. In eight experiments barium chloride was omitted, and concentrations of amphetamine sulfate from 1:1,000 to 1:2,000 caused an increase both in tonus and in amplitude of contraction waves in both layers of muscle (fig. 5 *A*), while more dilute concentrations (1:4,000) caused no noticeable change. The segment of rabbit ileum, on the other hand, lost considerable tone when exposed to 1:4,000 amphetamine sulfate and the rhythmic contractions were first inhibited and then abolished by comparable additions of the drug (fig. 5 *B*). In the presence of barium chloride the more dilute solution of amphetamine sulfate (1:4,000) caused varied results, but in concentrations above 1:2,000 rhythmic contractions were abolished with no change in tone.

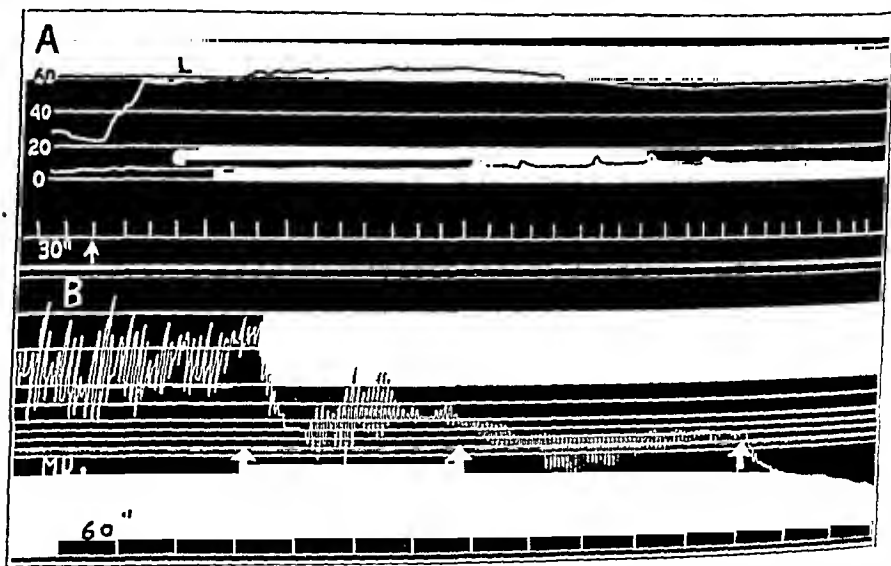


Fig. 5.—*A*, the stimulating effect on the excised human appendix of 1:1,000 amphetamine sulfate (arrow) in the absence of barium. There is a rise in tone in both layers, with a loss of rhythmic contractions in the outer layer, and an increase in contractions in the circular muscle. *B*, reduction in tone of a piece of rabbit ileum by the addition of amphetamine sulfate (1:4,000) to the water bath (200 cc.). Decrease in rhythmic contractions also occurred on further addition of the drug (second arrow, 50 mg.; third arrow, 100 mg.).

In the appendicostomy studies, 30 mg. of amphetamine sulfate was given by mouth in 3 instances, in 2 of which no effect could be seen. In the third instance this dose was administered ten minutes after 12 mg. of morphine sulfate had been injected subcutaneously. Some hyperactivity from the morphine had already appeared, but in another fifteen minutes greater activity became apparent in both the cecum and

23. The amphetamine sulfate was supplied by Smith, Kline & French Laboratories, Philadelphia.

the appendix than was evident on any other occasion in which morphine was given; the basal level dropped to below 20 cm. of water for six minute periods, alternating with periods of equal length during which violent rapid waves were present, the change lasting over an hour.

The findings with regard to this drug differ considerably from any found in the literature thus far, although Beyer¹² found that it caused a preliminary increase in tonus and rate of rhythmic contraction, followed in a few minutes by inhibition of contractions and return of tonus to normal. The startling difference between the response of the human appendix and that of the ileum of the rabbit, together with the prolonged hyperactivity of the appendicostomy specimen when morphine in conjunction with amphetamine had been administered, strongly suggest that there is here a difference between the response of the appendix and that of the remainder of the intestinal tract.

5. Acetylcholine: Acetylcholine hydrobromide in a concentration of 1:1,000,000 in the bath caused a moderate rise in resistance to flow and marked shortening of the specimen, with temporary disappearance of most of the big waves in both layers.

Ten milligrams given subcutaneously to a patient with an appendicostomy resulted in a great enlargement in the pendular and small tonus waves for over thirty minutes, with an elevation of the basal pressure of some 10 cm. for several minutes.

6. Physostigmine: This drug (physostigmine sulfate) was used only in the water bath, where in 10 specimens all concentrations from 1:20,000 to 1:4,000 caused increased tone in both layers of muscle, although the effect of the smaller doses was transitory. Smaller concentrations served as a stimulus to rhythmic contractions, in some cases even starting them when the specimen had been quiet previously, but higher concentrations seemed to interfere with motility.

7. Pilocarpine: Pilocarpine hydrochloride also was used only in the bath. In 4 specimens a concentration of 1:200,000 caused an increase in tone in both layers of muscle with a decrease in the size of the waves, and in 1 case a concentration of 1:50,000 caused shortening and loss of rhythmic contractions in both layers. These results are not in harmony with those of Gunn and Whitelocke,^{7c} who found a concentration of 1:200,000 to stimulate spontaneous movement. The effect in the experiments reported here is very similar to that of the higher concentrations of physostigmine previously mentioned; it is as if rhythmic activity is inhibited because the stimulating action of the drugs prevents the muscle from relaxing between waves.

8. Atrophine: Atropine sulfate was studied in 6 water bath specimens. A concentration of 1:14,000 in 1 instance caused a slight increase in tonus and rate of rhythmic contractions in the longitudinal muscle

but no other suggestion of a stimulating action. Concentrations of 1:10,000 were adequate to nullify the effect of previously administered physostigmine or acetylcholine. A concentration of 1:7,000 caused a temporary loss of tone and activity in both layers. In a specimen in which activity had been stopped with increased tone by physostigmine (1:5,000) the addition of 1:1,000 atropine caused marked loss of tone and return of rhythmic contractions.

No effect on the resistance to outflow in the appendix was observed after the administration of 0.4 mg. of atropine sulfate to a patient with an appendicostomy.

The finding of a stimulating action caused by dilute solutions of atropine is in accord with the findings of Magnus on segments of cat ileum,^{4e} results which Holm^{7e} and Hara and Uehara^{7d} failed to confirm in studies of the surviving appendix. It must be noted, however, that the dose which proved to have some stimulating action in the appendix was one seventh of that which Magnus found effective. The statement that the abolition of rhythmic contractions by higher concentrations of physostigmine and pilocarpine might be due to failure to allow relaxation between waves is of interest in connection with the restitution of rhythmic activity and the relaxation of the muscle brought about by the addition of atropine after higher concentrations of physostigmine had been exhibited.

9. Nicotine: Pure nicotine could not be obtained, but a crude preparation was used ("black leaf 40"), in concentrations from 1:12,000 to 1:120,000 in three water bath experiments. Addition of the drug to the water bath was followed by an immediate rise in tone in both layers and a simultaneous loss of rhythmic contractions. In two to three minutes the tone returned to normal and the rhythmic contractions recommenced in spite of the continued presence of the drug. These results are in essential agreement with the findings of Magnus,^{4e} except that he observed no change in tonus immediately but only a gradual shortening in half an hour or more.

10. Morphine: In very dilute solutions morphine sulfate was without effect in three water bath experiments, but when a concentration of 1:7,000 was used (once with and once without barium) an initial slight relaxation of the longitudinal muscle was followed by marked shortening of both layers lasting less than a minute; the tone fell to less than the initial level within ten minutes, and nearly all waves were abolished at once (fig. 6).

Twelve milligram doses of morphine sulfate were administered on three occasions to patients with appendicostomies. Twice there was a quieting effect on the appendical activity, the higher waves being diminished in one instance and the peaks of activity being eliminated

altogether in the other. In the latter instance cecal activity increased until the general cecal pressure was at least as high as that of the appendix, a situation nowhere else encountered in these experiments. On a third occasion there was a rise in appendical resistance with parallel increase in cecal activity of marked degree (fig. 3*A*).

The variability in the reaction to morphine in different subjects is less striking than the fact that two of the trials were on the same person, one causing definite stimulation and the other inhibition of movements.

11. Papaverine: In concentrations from 1:9,000 to 1:12,000 papaverine hydrochloride was effective in the water bath in stopping rhythmic contractions of the appendix without appreciable change in tonus regardless of whether barium had been added (fig. 4*A*).

A 30 mg. dose of the drug administered intravenously was without effect on the resistance to flow in an appendicostomy preparation.



Fig. 6.—Kymographic record showing transitory contraction followed by loss of tone and most of movements of both layers of muscle of a surviving appendix induced by the addition (arrow) of morphine sulfate to a concentration of 1:7,000.

12. Prostigmine: Subcutaneous injection of 0.5 mg. of prostigmine methylsulfate caused a prolonged period of increased resistance to flow in an appendicostomy preparation, with increased size of the pendular and small tonus waves. Thirteen minutes later increased cecal activity also became evident. The effect was still plainly visible over an hour later.

Prostigmine was not used in the water bath.

13. Amyl Nitrite: The inhalation of amyl nitrite was without evident effect on two occasions, although the systemic reaction was pronounced.

14. Spinal Anesthesia: Seventy-five milligrams of procaine hydrochloride dissolved in 3 cc. of spinal fluid was given intrathecally to 1 patient. With the onset of anesthesia the basal level became elevated about 8 cm., returning to the original level of 35 cm. as sensation com-

menced to return thirty-five minutes later. Coupled with this change was a decrease in the eminence of the large tonus waves, which unfortunately had not been well marked initially.

15. Cocaine and Procaine: Masson²⁴ had described a "plexus of the intestinal mucosa" related to the argentaffin cells of the mucous membrane of the intestine and appendix. He enlarged on the "musculoneural" mechanism of the submucosal portion of the appendix.

In order to determine if either of these structures plays a role in the maintenance of a resistance to flow of fluid through the lumen of the organ, attempts were made to anesthetize, if possible, the nerves involved. With a moist chamber at 37 C. instead of a bath, cocaine hydrochloride solution was applied topically to 4 specimens and run into the lumen of another. A 0.5 per cent solution applied to the serosa increased the resistance to flow, while higher concentrations reduced it and caused relaxation of the longitudinal muscle, results in harmony with those described by Cushny,²⁵ which, he stated, were due to direct action on the muscle. Five cubic centimeters of a 2 per cent solution run through the lumen in five minutes caused no change of tone in either layer.

Instillation of 5 cc. of a 1 per cent solution of cocaine hydrochloride in an appendicostomy preparation over a five minute period was followed by no definite effect except that on several subsequent peaks of activity the pressure rose 30 to 40 cm. of water higher than the peaks before the administration of the drug. A 3 per cent solution of procaine hydrochloride introduced in similar fashion had no effect except a lowering of the basal level 6 to 7 cm.

C. *Comparable Experiments on the Human Ureter.*—In 1 instance a ureter was obtained from a patient undergoing nephrectomy because of a malignant growth. Contractions of the longitudinal muscle shortened the specimen 6 to 7 per cent of its length every forty to fifty seconds, and the pressure curve was smooth at 8 cm. except for the spikelike rises to 25 to 30 cm. synchronous with the contractions of the longitudinal muscle. Active movement persisted almost five hours and was uninfluenced by the addition of 0.37 mg. of prostigmine methylsulfate or of 6 mg. of pilocarpine hydrochloride to the 180 cc. bath. One milligram of atropine sulfate slowed the rate of contraction somewhat,

24. Masson, P.: (a) Carcinoids (Argentaffin-Cell Tumors) and Nerve Hyperplasia of the Appendicular Mucosa, *Am. J. Path.* 4:181, 1928; (b) Contribution to the Study of the Sympathetic Nerves of the Appendix: The Musculoneuronal Complex of the Submucosa, *ibid.* 6:217, 1930.

25. Cushny, A. R.: *A Textbook of Pharmacology and Therapeutics*, Philadelphia, Lea & Febiger, 1928.

and 1:180,000 epinephrine hydrochloride caused slight shortening and a slight increase in rate of movement.

In 2 patients in whom nephrectomy was being performed a fine catheter was tied into the upper end of the remaining lower portion of the ureter, and studies were performed similar to those just described for the appendix. The catheter in each case was uneventfully withdrawn after a few days.

In each of these subjects the basal pressure was 6 to 8 cm. of water above the level of the ureter. In 1 (in whom the ureter was edematous and inflamed) there was a rise to approximately 20 cm. for a few seconds every five minutes; in the other, fine waves every three to five seconds were present, with peaks to 25 to 30 cm. of water every two to three minutes. Inhalation of amyl nitrite was without effect in either case, and subcutaneous injection of 0.67 cc. of a 1:1,000 solution of epinephrine hydrochloride subcutaneously also caused no change in either tracing except for an increase in the frequency of waves in the first subject. Twelve milligrams of morphine sulfate and one therapeutic ampule of prostigmine methylsulfate (0.5 mg.) were each without effect on the tracing of the second patient; but 1 cc. of solution of posterior pituitary of double the U. S. P. strength made the waves irregular, small and frequent, with some elevation of the basal level, and 10 mg. of acetylbetamethylcholine also rendered the peaks more frequent and elevated the basal level 2 to 3 cm. of water.

VII. CRITICAL REVIEW OF DATA ON THE ABSOLUTE RESISTANCE TO OUTFLOW (OF FLUID THROUGH THE APPENDIX INTO THE CECUM) AND ITS RELATION TO DISEASE OF THE APPENDIX

A. *Introduction.*—Reports on the correlation of the operative diagnosis with the absolute resistance to outflow (of fluid through the appendix into the cecum) determined at appendectomy have already been published,²⁰ and it has been indicated that the resistance is elevated, as a rule, in appendicitis. In order to control the determinations more rigidly, a series of readings has been correlated with the combined surgical and microscopic diagnosis, no case having been considered normal except those in which history, results of physical examination and operative and microscopic observations all were normal.

B. *Procedure.*—At the time of appendectomy a no. 19 needle was inserted into the distal lumen of the exposed appendix. The needle was connected by rubber tubing to an elevated flask of isotonic solution of sodium chloride fitted with a gravity drip bulb and adjusting valve

26. Wangensteen, Buirge, Dennis and Ritchie.²² Wangensteen and Bowers.²

and with a manometer of fine bore. The flow of fluid was adjusted to a rate of 60 drops per minute, the fecal matter washing out of the appendix and into the cecum. The flow was then stopped, and the level above the appendix to which the manometer meniscus fell was termed the "absolute resistance to outflow."

C. *Evaluation of Variations in Resistance to Flow Introduced by Muscular Contractions During Determinations.*—In many instances it was necessary to divide the mesentery before insertion of the needle, and in others, especially with acutely inflamed specimens, the determination could not be made until after removal of the appendix. In 14 instances determinations were made before section of the mesentery and also afterward, or before and after amputation, or both. The mean arithmetic difference between values of water pressure before and after surgical intervention in this group was 9.7 cm., and in only 3 instances did it exceed 15 cm. The algebraic mean was 4.4 cm.

In several instances the length of the specimen as well as the change of resistance to flow with surgical intervention was determined in order to check the possibility that the change in resistance might be due to general contracture of the appendical musculature. There was no correlation between the changes in length and the changes in resistance to flow either with section of the mesentery or with amputation of the specimen. It therefore seems most likely that the variations are due to the incidental occurrence of the large tonus waves previously described, which are of adequate size easily to account for the discrepancies observed.

In confirmation of this conclusion, rhythmic variations in the resistance to outflow with fluid running at 60 drops per minute were commonly seen. The amplitude of these waves varied from 2 to 18 cm. of water pressure. The activity of the muscle even in the presence of the trauma necessarily inflicted was demonstrated also by faradic stimulation with a technic similar to that described elsewhere for experiments with apes^{1b}; elevations of resistance from 43 to 68 cm. occurred in 1 case and from 34 to 76 cm. in another.

D. *Correlation of the Absolute Resistance to Outflow with the Clinicopathologic Diagnosis.*—The determinations for 70 specimens are presented in table 2. The mean resistance to outflow of 6 normal appendixes was 26 cm. of water. In 15 interval specimens the mean was 31.5 cm.; in 7 with fibrosis it was 54 cm., and in 8 shown microscopically to have residual inflammation it was 50 cm. In 11 appendixes showing minimal inflammation the mean was 68 cm. of water, and in 10 with more advanced inflammation it was 82.3 cm. In 13

specimens from the morgue, on the other hand, the resistance was insignificant, indicating the great importance of the muscular factor.

Inspection of the column of standard deviations from the mean of each group in table 2 shows that appendixes presenting a normal cytologic picture vary relatively little from a mean of about 30 cm., while the variability is greater in the acutely inflamed appendixes and most marked in the fibrosed interval specimens. The calculations of probable error show that the differences between normal and inflamed organs are statistically significant even in view of the variations due to large tonus waves.

TABLE 2.—*Correlation Between Present or Past Inflammation and Absolute Resistance to Outflow Determined in the Operating Room**

Appendix	Number of Cases	Absolute Resistance to Outflow (Pressure Measured in Centimeters of Water)				
		Mean	Standard Deviation from Mean †	Probable Error from Mean †	Maximum	Minimum
Specimens from morgue.....	13	3	1.75	0.49	7	0
Normal.....	6	26	3.5	1.4	29	19
Interval specimens with normal cytologic picture.....	15	31.5	11.5	3.0	63	18
Interval specimens with fibrosis.....	7	53.6	48.0	18.1	120‡	0§
Interval specimens with some inflammation persisting.....	8	50	31.4	11.1	120‡	20
Minimally inflamed.....	11	68	36	10.9	120‡	20‡
"Acute suppurative".....	10	82.3	36.3	11.5	120‡	30‡

* In the instances in which the absolute resistance to outflow was determined before and after section of the mesentery or amputation, the mean of the values obtained was used.

† Standard deviation = $\sqrt{\frac{1}{N}(M - V)^2}$. Probable error = $\frac{1}{N}\sqrt{(M - V)^2}$. In these formulas N stands for the number of cases, M for the mean and V for any individual value.

‡ As the apparatus used most of the time would record no higher than 120 cm., this value was assigned when no flow occurred at this level.

§ Narrowing throughout the lumen; the pressure was 80 cm. at 20 drops per minute.

‡ Postoperative determination; Some question exists as to whether amputation was at the true base or distal to the supposed obstruction.

VIII. EVALUATION OF THE ROLE OF NEUROMUSCULAR ACTIVITY IN INITIATING ACUTE APPENDICITIS

A. *Introduction.*—Wangensteen and I^{1a} have shown that obstruction of the lumen of the normal human appendix results in elevation of the intraluminal pressure in the neighborhood of 80 to 120 cm. of water due to the secretion of fluid by the mucosa, with the development of ischemic necrosis and acute suppurative appendicitis. In the chimpanzee we have shown that this process, if not interrupted, will go on to gangrene and perforation.^{1b} The importance of the muscular function will be established, therefore, if it can be shown to offer this degree of obstruction.

B. *Proof of the Existence of Cases of Acute Appendicitis with Spastic Obstruction to the Lumen.*—Appendixes each with an absolute resistance to outflow of 50 cm. of water or more in the operating room were subsequently fixed in 4 per cent solution of formaldehyde and sectioned longitudinally in search of organic obstructions. The observations are presented in table 3. It is evident that although organic obstruction was responsible wholly or in part for the elevation in resistance to outflow in 11 of 15 cases, in 4 cases it apparently played no part. In the 6 cases in which there was narrowing of the lumen a

TABLE 3.—*Evidence of Functional Obstruction: Absolute Resistance to Outflow Contrasted with Degree of Obstruction Visible on Longitudinal Section After Fixation in Formaldehyde Solution **

	Absolute Resistance to Outflow (Pressure Measured in Centimeters of Water)		
	With No Obstruction Seen After Fixation	With Narrowing of Lumen Seen After Fixation	With Complete Obstruction Seen After Fixation
Acute suppurative appendicitis.....	100 cm.†	53 cm. 63 cm.‡ 110 cm. 110 cm.	124+ cm. 200 cm. 900 cm.§
Subsiding appendicitis.....	52 cm.	51 cm.‡ 112 cm.	
Interval specimen.....	63 cm.		
Interval specimens with fibrosis.....	77 cm. 120+ cm.

* This table is limited to specimens showing an absolute resistance to outflow above 50 cm. of water. Each number represents the absolute resistance to outflow of one specimen in situ or within two minutes after amputation.

† This value was determined after amputation of the appendix and therefore cannot have been due to amputation distal to the site of obstruction.

‡ The narrowing was found only in the distal portion of the appendix, the inflammation throughout.

§ "Acute and chronic granuloma."

|| The presence of elevated resistance to outflow in the absence of acute appendicitis will be discussed in section XII.

functional element must also have been present to cause a resistance to flow of the order of 50 cm. of water.

In order to show that these high values rest in fact on muscular action and not on an anatomic change overlooked on longitudinal section after fixation, evidence may be gathered from a comparison of the resistance to outflow of freshly excised appendixes with that of specimens studied after loss of tone in the muscle. In 32 unfibrosed specimens presenting varying degrees of inflammation, the mean resistance to outflow within a few minutes after removal from the patient was 45 cm. of water; more than a half-hour later the mean was 9 cm. It is evident, therefore, that at least 80 per cent of the resistance to

flow in this group was due to muscular activity; indeed, comparison with the values obtained from the specimens from the morgue (table 2) indicates that almost all the usual resistance is muscular in origin.

C. *Question of Physiologic Sphincter Action at the Base.*—It has already been reported that neither the mucosal folds around the appendicocolic orifice nor the muscular arrangement at the base of the appendix presents an anatomic basis for obstruction to the lumen,²² but the possibility remains that the muscle in this region is capable of sphincter-like behavior.

A considerable number of appendixes was studied immediately after operation by incannulation of the tip and amputation of successive seg-

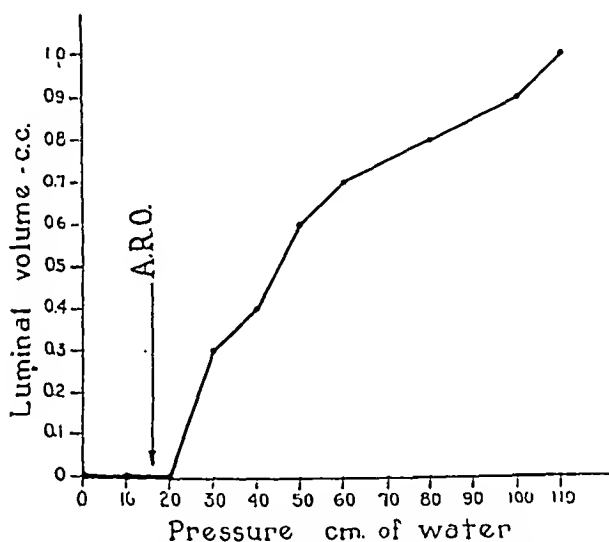


Fig. 7.—Graph made from data obtained from studies of an appendix in situ, illustrating the relation of the luminal volume to the intraluminal pressure. This volume uniformly remains zero in the normal appendix until the pressure is higher than the absolute resistance to outflow.

ments from the base to determine the effect on the resistance to outflow. By insertion of long, slender cannulas varying distances into the lumen of other fresh specimens, further information was obtained. In both types of experiment the appendix was found irritable, the resistance rising with each new manipulation. To test the full possible extent of such change, one specimen was excessively manipulated, and the resistance rose from 16 to 60 cm. in four minutes.

The most satisfactory method of approach to the problem proved to be determination of the luminal volume at varying levels of intraluminal pressure. For this purpose the tip of the appendix was incan-

cated by the fact that in many specimens the rate became fast and feeble as the muscle failed, but an attempt was made to make calculations from each tracing at a point when full activity had been established and failure had not yet begun. Figure 8 illustrates the comparative activities of separate segments of an interval specimen.

If the site of fastest rhythmic contractions is correlated with the clinicopathologic diagnosis, a fairly consistent picture is obtained. In the only normal specimen of this series this site was at the tip; in 2 of the other 3 uninflamed specimens it was also in the distal half, while in 8 of the 9 specimens showing acute inflammation the segment showing fastest rhythmic contractions was either at the middle of the specimen (in 3) or in the proximal half. Unfortunately the absolute resistance to outflow of these appendixes was not determined in the operating room, but none showed organic obstruction. The suspicion arises, therefore, that hyperactivity in the proximal portion may have been a factor in initiating the acute inflammation in most of the cases. A large series of normal patients should be studied before conclusive results can be expected.

As has already been reported,²² the propulsive activity of the appendix was studied in specimens made available by appendicostomy by insertion of pieces of bird shot, most of which passed in a few hours into the cecum. In several instances small amounts of feces were found on the appendicostomy dressings after the tip had been removed, in 1 instance in the same twenty-four hour period in which a shot was passing toward the cecum. It is evident, therefore, that such propulsive activity as is present is at times overcome or reversed.

IX. RELATION OF NEUROMUSCULAR ACTIVITY TO APPENDICAL PAIN AND THE EFFECT OF EPINEPHRINE ON IT

Most writers on appendical pain agree that the initial poorly localized pain is due to muscular tension in the appendical wall.²⁷ One school of thought ascribes the localized later pain to parietal peritoneal

27. (a) Alvarez, W. C.: Abdominal Pain: II. The Sensitive Regions in the Abdomen and Ways in Which They May Be Stimulated to Produce Pain, *J. A. M. A.* **102**:1351 (April 28) 1934. (b) Gray, S. H., and Heifetz, C. J.: Lymphoid Hyperplasia of the Appendix with a Note on Its Rôle in Acute Appendicitis, *Arch. Surg.* **35**:887 (Nov.) 1937. (c) McCloskey, B. J.: A Review of Certain Diseases of the Appendix Clinically Called Chronic Appendicitis: Physiology of Appendiceal Movements, *Internat. Clin.* **2**:101, 1937. (d) MacKenzie, J.: Symptoms and Their Interpretation, London, Shaw & Sons, 1920. (e) Morley, J.: Abdominal Pain as Exemplified in Acute Appendicitis, *Brit. M. J.* **1**:887, 1928. (f) Williams, O. T.: Abnormal Fat Assimilation Associated with Some Diseases of the Intestine, *Biochem. J.* **2**:395, 1906; (g) The Microchemical Change Occurring in Appendicitis with a Note on the Incidence of the Disease in Various Countries, *ibid.* **3**:391, 1907.

involvement (McCloskey²⁸ and Morley²⁹), and another to reference by reason of proximity of visceral and somatic sensory routes in the upper part of the lumbar region of the spinal cord (MacKenzie^{27d}).

In subjects with an obstructed, extraperitonealized appendix^{1a} pain is often experienced, sometimes in the umbilical region but usually in the right lower quadrant. In 1 case the pain in the right lower quadrant could be alternately reproduced and relieved by elevating and lowering the intraluminal tension.

Distention of the artificially obstructed appendix with saline solution, by means of a hypodermic needle inserted into the lumen at the time of appendectomy, was performed under local anesthesia four times.^{2a} In 1 instance a pressure of 170 cm. of water drew a complaint from the patient of "pain in the pit of the stomach"; higher pressures caused umbilical pain in 2 others, followed in 1 instance in three minutes by reference of pain to the right lower quadrant and in the other by pain in the right lower quadrant followed by nausea.

The type of bilateral pain in the lower part of the abdomen described by Wilkie²⁹ was seen in 1 patient with an unobstructed appendix made available by appendicostomy in whom crampy pains occurred in both lower quadrants during the passage of a bird shot through the lumen into the cecum. Two clinical patients with the same type of cramps proved to have a small concretion and an ingested piece of bird shot respectively in the appendical lumens.

Because of the action of epinephrine in relaxing the circular muscle of the appendix, 0.33 to 0.5 cc. doses of a 1 : 1,000 solution of epinephrine hydrochloride were injected subcutaneously into 9 patients with supposed acute appendicitis. Seven obtained complete or partial relief, and 2 did not. Of these 2, 1 proved to have acute suppurative appendicitis, and the symptoms in the other were subsequently shown to arise from ureteral obstruction. All those whose symptoms were relieved by the drug had appendical cause for their symptoms (table 5).^{29a}

28. Dr. W. F. Bowers collaborated in the prosecution of these observations.

29. Wilkie, D. P. D.: Acute Appendicitis and Acute Appendicular Obstruction, Brit. M. J. 2:959, 1914.

29a. Since submission of this paper for publication, placebos and epinephrine have been administered to a group of patients to try to obtain adequate control observations. The results indicate that some patients with other complaints obtain relief, as would be expected with intestinal spasm in some diarrheas. Some patients also failed to obtain relief in the presence of appendicitis (6 out of 22 patients). The series of administrations of placebo is too small to allow conclusions on a statistical basis, but the occasional case of acute suppurative appendicitis in the absence of organic obstruction in which almost complete relief was obtained from injections of epinephrine is very impressive.

Specimens from 7 of these 9 patients were sectioned longitudinally after fixation in solution of formaldehyde, and 4, from patients whose symptoms were partially relieved by the epinephrine, presented no narrowing of the lumen or obstructing fecalith.

X. CONTRIBUTION OF THE OBSTRUCTIVE THEORY OF APPENDICITIS
TO THE EXPLANATION OF PERITONITIS IN CERTAIN CASES;
DATA ON SEEPAGE THROUGH THE APPENDICAL WALL

In the course of intraluminal tension studies seepage through the appendical wall was often observed. In order to study the nature of

TABLE 5.—*The Effect of Epinephrine on Pain Due to
Supposed Acute Appendicitis*

Patient	Age	Dose of Epinephrine Hydrochloride (1:1,000), Cc.	Pain Relief	Final Diagnosis	Status of Lumen of Fixed Specimen (Longitudinal Section)
1	25	0.50	Complete	Appendical colic	Lumen normal; shot-like fecaliths
2	23	0.50	Considerable	Appendix almost gangrenous	Stenosis and fecalith
3	16	0.50	Partial	Acute appendicitis; peritonitis	Not sectioned
4	19	0.33	Almost complete	Late subsiding appendicitis	Normal
5	13	0.33	Partial	Subsiding acute appendicitis	Normal
6	58	0.33	Partial	Mild acute appendicitis	Normal
7	18	0.33	Slight	Acute appendicitis	Not sectioned
8	12	0.33	None	Acute suppurative appendicitis	Narrowed at base
9	27	0.33	None	Mild acute appendicitis *	Small fecalith near tip; slight distension beyond

* Unaltered pain continued after appendectomy and was proved later to be due to ureteral colic.

this seepage more carefully, methylene blue solution was used, and the specimen was observed against a white background. Seven specimens were studied in the operating room immediately after amputation; the mean level of pressure at which seepage of fluid occurred was 92 cm. of water, the maximum 125 cm. and the minimum 60 cm. Seventeen others tested after being in the ice box gave similar results. In the usual case the seepage came from the general appendical wall and was colorless, but in a few cases in which the condition was acute the superficial vessels in some areas became engorged with the blue fluid and colored seepage occurred. In many cases the mesenteric lymphatics were also filled.

In 1 specimen, classified as showing "subsiding acute" appendicitis, the serosa was kept sterile after removal and during the determination

of the seepage level. Cultures of material taken from the surface after seepage had occurred at 100 cm. showed the presence of luminal organisms, in contrast to sterile control cultures prior to elevation of the pressure.

XI. RELATION OF INCREASED INTRALUMINAL TENSION TO RUPTURE

In order to determine the bursting strength of excised appendixes, 66 specimens were subjected to intraluminal pressures ranging up to 2,400 cm. of water (2.3 atmospheres). In 19 specimens this was not adequate to cause rupture; in 39 the pressure could not be raised this high because of rapid seepage, and in only 8, all presenting far advanced or gangrenous appendicitis, did rupture occur. In 1 gangrenous specimen this occurred at a pressure of 20 cm. of water. Maintenance of 1 atmosphere of pressure for ten days at room temperature also failed to rupture an uninflamed interval appendix. Preliminary incubation at 37 C. for one and three days respectively followed by submission to 2.3 atmospheres also failed to rupture 2 uninflamed appendixes.

XII. APPLICATION OF THE OBSERVATIONS ON NEUROMUSCULAR ACTIVITY TO THE GROSS AND MICROSCOPIC PATHOLOGIC OBSERVATIONS

A. *Comparison of the Clinicopathologic Diagnosis with the Degree of Luminal Obstruction Found on Longitudinal Section After Fixation in Solution of Formaldehyde.*—Review of the gross and microscopic observations on the appendixes used in this study throws some light on the difficulties involved in general application of the theory of the etiologic relation of luminal obstruction to acute appendicitis.

In 93 instances, comprising two series of consecutive cases, the specimens fixed in solution of formaldehyde were sectioned longitudinally in search of organic obstructions preliminary to the routine preparation of sections stained with hematoxylin and eosin for microscopic examination.

All gangrenous specimens showed complete obstruction of the lumen, as Wangensteen and Bowers² had found (fig. 9). Ten of 24 acutely inflamed specimens showed at least some degree of obstruction, and 2 showed partial obliteration of the distal lumen. The situation was similar in cases of mild appendicitis, while in the cases of subsiding appendicitis 20 out of 23 specimens showed no evidence of luminal obstruction. There were several cases, however, in which the degree of inflammation, as seen by both the surgeon and the microscopist, was mild or nonexistent and either complete obstruction or a high

degree of obstruction was evident (in several of these cases the resistance to outflow was found to be high).

B. Demonstration of an Abnormal, Nonsecreting Mucosa in Minimally Inflamed or Uninflamed Appendixes with Complete Obstruction.—In 6 cases of complete anatomic obstruction (black circles in figure 9) and in 5 cases of physiologic obstruction of marked degree, as indicated by a high resistance to outflow, microscopic studies were made, and in each instance the mucosal epithelium was found to be abnormal. In some instances it was entirely absent or entirely replaced by fibrous tissue, and in others a degree of subacute inflammation was evident with marked disruption of the secreting surface (fig. 10 A).

Demonstration of loss of secretory power in such circumstances is indicated by 1 case in which appendicostomy was done and in which

	Complete fibrous obstruction	Fecalith-stenosis complete obstruction	Stenosis	Free fecalith	Partial obliteration of lumen	Patent lumen
Gangrene	ooo	oo				
Acute diffuse appendicitis	oooo	oo	oooo			oooooo oooooo
Mild acute appendicitis	o.		ooo	o		ooooo
Subsiding appendicitis	..		o			ooooooo ooooooo ooooooo
Interval with inflammation	.					o
Interval with fibrosis	..		o			ooooooo
Other interval			ooo	oo	oo	ooooo
Normal microscopically						oo

Fig. 9.—Graph showing the correlation between the patency of the lumen of the human appendix, as determined by longitudinal section after fixation in solution of formaldehyde, and the clinicopathologic diagnosis. The black circles indicate persons with abnormal mucosa (see text and figure 10 A).

unsuspected stenosis was present proximally. Acute appendicitis, proved by microscopic study of the amputated tip, developed with the appendix in the new site and was completely relieved by drainage of the distal lumen. No evidence of fluid secretion could be demonstrated by either the collection or the manometric method.³⁰ After the patient was dismissed from the hospital, however, secretion recommenced, and the appendix was removed seven months later for this reason; the distal mucosa now was normal in appearance (fig. 10 B); the recovery was comparable to that seen in the rabbit after relief of obstruction.³¹

30. Wangenstein, Buirge, Dennis and Ritchie.²² Wangenstein and Dennis.¹²

31. Buirge, R. E.; Dennis, C.; Varco, R. L., and Wangenstein, O. H.: Histology of Experimental Appendical Obstruction (Rabbit, Ape and Man). Arch. Path. 30:481 (Aug.) 1940.

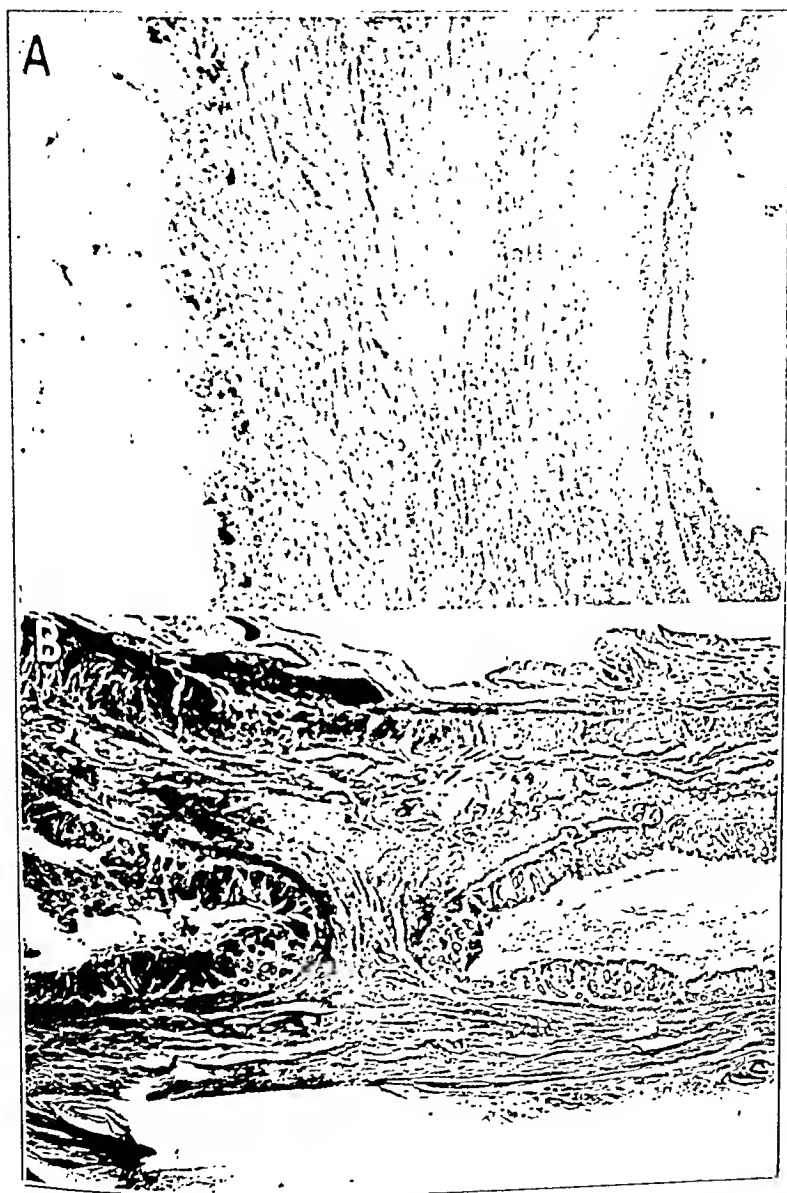


Fig. 10.—Photomicrographs. *A*, marked abnormality of the mucosa distal to a complete obstruction. Subsiding inflammation is present. Both the epithelium and the glands have been lost. (Hematoxylin and eosin stain; $\times 60$.) *B*, an appendix removed seven months after appendicostomy. In the first few days after appendicostomy acute appendicitis developed and was relieved by drainage of the distal lumen; the resistance to flow eight hours later was 85 cm. of water, and roentgen ray examination with the aid of iodized poppyseed oil showed an area of stenosis in the proximal portion of the appendix; obstruction was therefore incomplete. Complete fibrous obstruction developed in the intervening months, and normal mucosa is present distally (at the right). (Azocarmine stain; $\times 10$.)

C. *Development of Complete Organic Obstruction Following Acute Appendicitis.*—In the case mentioned in the preceding paragraph, roentgenologic study with iodized poppyseed oil a few days after amputation of the tip of the appendix for relief of appendicitis showed two marked constrictions near the base, but the resistance to flow at that time was below 100 cm. of water pressure. When the specimen was removed seven months later, the obstruction was physiologically and anatomically complete (figure 10 B). It is suggested but not conclusively proved that the inflammatory reaction led directly to additional fibrosis and complete obstruction.

D. *Acutely Inflamed Appendixes Presenting No Anatomic Obstruction.*—As figure 9 indicates, 38 specimens presented a greater or less degree of active or subsiding appendicitis with no obstruction demonstrable on longitudinal section after fixation in solution of formaldehyde. Although it is possible that evidence of stenosis would have been found more often if the appendixes had been opened in the fresh state, as Williams and Boggon recommended,³² the presumed obstructive factor in these specimens must have rested primarily on the functional basis previously shown to exist.

E. *The Relation of Luminal Content to Luminal Volume and Diagnosis.*—In 24 specimens the luminal content of the chilled specimen was expressed and weighed. The appendix was thereafter incannulated and brought to body temperature for determination of the volume at 20 cm. of water pressure. No correlation was found between the magnitude of the luminal content and either the pathologic condition of the specimen or the volume at 20 cm. of water pressure, with the reservation that the only 3 specimens containing more than 0.5 Gm. of material had a luminal volume of over 0.5 cc. at 20 cm. In this group of 24 specimens, the 10 with a definite luminal volume at 20 cm. of water pressure were acutely inflamed.

PART 3. INTEGRATION OF OBSERVATIONS

XIV. COMMENT

A substantial part of the argument of Aschoff and his associates concerning the origin of appendicitis rests on stasis secondary to the supposed lack of active movements of the organ (Aschoff and Pokerny⁷² and Ruf⁷¹). The present study demonstrates active movements in over 90 per cent of normal specimens after excision and also marked activity in appendicostomy preparations, in reference both to changes in resistance to flow of fluid and to active propulsion of foreign bodies. As the present

32. Williams, B. W., and Boggon, R. H.: The Mechanics of Appendicitis. *Lancet* 1:9, 1934.

series is apparently larger than the organ seems well established factor in the causation of appendicitis.

Certain differences between *in situ* and after excision exist, and certain influences, nervous or vascular, on the appendix are suggested.

The responses to the administration of drugs throw some light on the factors involved in the resistance of the circular muscle of the appendix to the basal level of resistance. The tonus of the appendiceal circular muscle must be either intrinsic in nature or dependent on some extrinsic reflex. That the former is the case is indicated by the fact that although the level of the resistance to flow is only a fraction as high in those made available by appendicostomy, it is unchanged immediately after removal of the appendix in the operating room. It follows that the low resistance encountered in the water bath is lower than *in situ* because of impaired nutrition.

The instillation of cocaine into the lumen of an appendix made available by appendicostomy resulted in elevation of the peak levels of pressure, which must have been due to diffusion of the drug to the muscle itself, yet the nature of the circular muscular activity was not otherwise altered. Meissner's plexus, past which the cocaine must have diffused and which must have been exposed to a concentration of the drug at least equal to that in the muscle, therefore (1) must not be essential to the movements of the muscle, (2) must exert an inhibitory influence on tone or (3) must be insensitive to the drug.

On the whole, the responses of the appendix to a variety of drugs suggest that the mechanisms involved in those responses must be similar to those of the ileum; but with amphetamine and with morphine a qualitative difference is demonstrable, and with pilocarpine and with atropine much greater sensitivity was found in the appendix than has been reported for the ileum.

With regard to pain, localization in the right lower quadrant following a rise in intraluminal pressure, whether that rise occurs spontaneously in extraperitonealized artificially obstructed appendixes or is induced at appendectomy under local anesthesia, indicates that parietal peritoneal involvement is not always requisite to reference of pain. Bilateral colic in the lower part of the abdomen has been proved due to the presence of a foreign body in the appendiceal lumen in 3 cases. Occurrence of this type of pain, attributed by Wilkie to "obstructive appendicitis," during the passage of a shot through the lumen of an appendix made available by appendicostomy suggests that the pain is due to contractions

in the dog leads to acute inflammatory changes in the wall. The microscopic data from the ape and rabbit experiments,³⁵ which Koster and Shapiro failed to mention, showed clearly the relation of the development of increased intraluminal tension to the development of the classic microscopic picture of acute appendicitis. Aside from the few microscopic data presented, therefore, the demonstration of increasing intraluminal tension in obstructed human appendixes with intact mucosa is powerful evidence that obstruction in such organs leads directly to acute appendicitis.

The early changes of mucosal injury following sustained moderate elevation of intraluminal tension were observed by us in the rabbit.^{34a} In this species a pressure of less than 20 cm. of water maintained for twenty-four hours resulted in edema and disorganization of the mucosa, combined with diminished secretory capacity. More prolonged periods or more elevated pressures resulted in more marked changes, particularly in the development of acute inflammation. The findings in the human specimens presenting complete obstruction indicate that in man also the mucosa must be sensitive to prolonged increases in pressure and that the rate of secretion slows after the prolonged elevation of pressure due to some types of obstruction.

In the rabbit it was possible to relieve the obstructing mechanism, and the microscopic picture was found to return to normal in the course of a few hours.³¹ Similar mucosal recovery, as far as microscopic criteria are concerned, was observed in the case of an obstructed extra-peritonealized appendix in which free drainage onto the abdominal wall persisted after relief of an acute attack by amputation of the tip. The return of actual secretory function is testified by an obstructed, extra-peritonealized appendix in which the external fistula closed spontaneously with resultant and clinically typical appendicitis, cured by spontaneous reopening of the fistula.

If the facts found in this investigation are followed to their logical conclusion, the question whether an appendix in the early stages of acute appendicitis will become gangrenous and rupture, will subside spontaneously or will form a mucocele must depend on several factors. If the obstruction is complete and the mucosa actively secreting, then gangrene may be anticipated; but if the obstruction is spastic and therefore may be expected to allow escape of fluid at not too high a pressure, gangrene probably would not occur, for the mucosal injury produced by the sustained moderate pressure would inhibit further secretion after a time, and the process should then subside. If an appendix with already inhibited mucosa of such type should become completely obstructed, secretion might be expected to cease before rupture occurred, and mucocele should result.

It has been reported in previous papers that there is obstruction in most cases of appendicitis and that the disease may be experimentally produced by ligature obstruction in those species in which the organ secretes fluid.⁴⁰ In the preceding pages evidence has been presented that in certain cases the condition rests on obstruction of a muscular or functional nature rather than on organic occlusion and that organic obstruction may be the result of previous milder degrees of inflammation. It is evident, therefore, that early mild attacks of the disease may be followed by attacks of increasing severity as the degree of organic obstruction increases, terminating in an attack with complete obstruction and gangrene or, less often, mucocoele.

IV. CONCLUSIONS

1. Under proper conditions the excised surviving normal human appendix is capable of active rhythmic contractions of both circular and longitudinal layers of muscle. Inflamed specimens contract less well.
2. The resistance to flow of fluid through the lumen of the normal appendix in situ is due primarily to tones of the circular muscle, and rhythmic contractions of that muscle vary the resistance to flow.
3. The absolute resistance to flow of fluid offered by an incannulated normal appendix in situ is identical with the normal intraluminal tension. This is usually 15 to 30 cm. of water pressure, while that in the cecum is 2 to 5 cm.
4. At such pressures the normal human appendix has a luminal volume of less than 0.05 cc. There is no sphincter or sphincter-like action in the proximal as distinguished from the distal portion. A luminal volume greater than 0.05 cc. determined by the method described indicates a pathologic state.
5. Epinephrine relaxes the appendical but not the ureteral musculature.
6. Morphine and amphetamine produce responses in the appendix qualitatively different from those in the ileum, and pilocarpine and atropine show quantitative differences. The behavior of the appendix after administration of a variety of other drugs was found similar to that known for the ileum.
7. Inflamed appendixes present an average resistance to outflow (of fluid through the appendix into the cecum) three times normal, and that of interval specimens usually falls between.
8. Evidence is presented that acute suppurative appendicitis but not gangrene may be initiated by spasm of a portion of the muscular wall of the appendix. The stimulus for this spasm is not known.

40. Footnotes 22, 31 and 34.

9. Appendical pain, including the pain radiating to the right lower quadrant, is largely due to tension on the muscular wall of the organ and may usually be ameliorated by epinephrine.

10. Seepage of infected fluid through the appendical wall occurs at levels of intraluminal tension commonly reached in appendicitis. A ready explanation of many cases of peritonitis without rupture, such as those stressed by Allen,⁴¹ is therefore at hand.

11. Rupture during appendicitis is due to digestion of the wall, and the normal appendical wall can withstand an intraluminal tension of over 2 atmospheres.

12. Completely obstructed appendixes may remain uninflamed because of loss of secretory power of the mucosa. Associated microscopic changes are present.

41. Allen, R. B.: An Analysis of Certain Clinicopathologic Features of Disease of the Appendix, *Journal-Lancet* **52**:614, 1932.

LYMPHOSARCOMA OF THE PROSTATE GLAND

WITH REPORT OF A CASE

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Among primary malignant prostatic tumors, those of lymphoid origin are considered to be extremely rare. To date, however, a fair number of cases of so-called primary lymphosarcoma of the prostate gland have been reported, but the great majority of them have been discarded by recent investigators on the ground that insufficient clinical or histologic evidence was presented to justify the diagnosis. Since carcinoma is the most frequent type of primary malignant tumor of the prostate gland and since many of these prostatic new growths may be composed of primitive, highly undifferentiated cells, a majority of the tumors reported as lymphosarcoma have been looked on as highly anaplastic carcinoma which was called lymphosarcoma by mistake. A strong point in favor of the rarity of lymphosarcoma in this organ is the absolute paucity, not to say absence, of lymphoid tissue from which primary lymphosarcoma could arise. We shall come back to this point later and discuss its relative value in the diagnosis of prostatic tumors. For many investigators this argument is sufficient reason for excluding lymphosarcoma from the list of the possible types of primary malignant tumor of the prostate.

Symmers¹ claimed that only 1 reported case of primary prostatic lymphosarcoma, that of Coupland,² could be accepted without question.

Coupland's patient was a 29 year old man who four years previously had suffered from acute gonorrhea complicated by orchitis and a syphilitic chancre. When the patient came to autopsy, two months after the first observation of symptoms, a fleshy prostatic tumor, 20.3 cm. in circumference and 8.9 cm. in length, was found. The new growth had surrounded the neck of the bladder and the prostatic urethra, had invaded the base of the bladder in the region of the median lobe and had metastasized to the pancreas and the right adrenal gland.

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1. Symmers, D.: Primary Lymphosarcoma of the Prostate, *Arch. Surg.* 6:755-763 (May) 1923.

2. Coupland, S.: Lymphoma (Lymphosarcoma) of the Prostate: Secondary Nodules in Pancreas and Supra-Renal Capsule, *Tr. Path. Soc. London* 28:179-185, 1877.

Symmers himself studied 1 case at Bellevue Hospital in New York, that of a 30 year old man, whose clinical history and pathologic findings were almost identical with those of Coupland's patient. He felt that such tumors "are not so rare as the literature would indicate." He subsequently ventured the opinion that lymphosarcoma should always be considered a possibility in patients under 35 years of age who suffer from prostatic hypertrophy.

In the opinion of Ferguson and Stewart,³ Symmers' case and 3 reported prior to it can be accepted as cases of primary lymphosarcoma of the prostate gland. One of the 3 was Coupland's case. The second was that described by E. Kaufmann.⁴

The patient was a 24 year old aniline worker. The tumor had apparently arisen around the trigone of the bladder and, besides infiltrating the urethra and the right seminal vesicle, had metastasized to the pleurae, kidneys, pancreas, dura mater, cervical lymph nodes, tibia, calvarium and one small lymph node in the pelvis. Histologically, the neoplasm was diagnosed as lymphosarcoma. It was composed of small lymphoid cells, embedded in a finely reticular stroma.

Although Ferguson and Stewart accepted the diagnosis of lymphosarcoma in this case, the evidence presented was not satisfactory to Ewing. The third case was that of a 41 year old farmer, reported by Quinby,⁵ in which a diagnosis of lymphosarcoma of the prostate gland was made by biopsy. This patient became rapidly emaciated and died five months after the onset of the first symptoms, with generalized metastases. Autopsy was not done.

Ferguson and Stewart themselves presented a fifth case which was accepted by the Lymphatic Tumor Registry of the American Association of Pathologists and Bacteriologists as "true lymphosarcoma."

This new growth involved the prostate gland, bladder and seminal vesicles and metastasized to the pelvic, aortic, abdominal and inguinal lymph nodes and to both kidneys. It occurred in a 36 year old white man, who thirteen years before his present illness had suffered from gonorrhea with marked posterior urethritis. Six months prior to his admission to the hospital he had lost 30 pounds (13.5 Kg.) in weight. For the last seven weeks of this period nocturia with increasing frequency but without burning, tenesmus or hematuria was the main symptom. One week before admission he had an attack of acute urinary retention. The blood chemical findings were within normal limits, but the urine showed albumin and a large amount of pus. An operation was performed, and the specimen removed was reported as carcinoma. When the patient was referred to the Memorial Hospital for the Treatment of Cancer and Allied Diseases, in New York.

3. Ferguson, R. S., and Stewart, F. W.: Lymphosarcoma of the Prostate. *J. Urol.* 28:93-104, 1932.

4. Kaufmann, E., in Socin, A., and Burckhardt, E.: *Die Verletzungen und Krankheiten der Prostata*, in Billroth, T., and Luecke, G.: *Deutsche Chirurgie*. Stuttgart, Ferdinand Enke, 1902, no. 53, pp. 394-395.

5. Quinby, W. C.: Lymphoblastoma (Lymphosarcoma) of the Prostate. *J. Urol.* 4:137-144, 1920.

rectal examination disclosed a hard irregular tumor, 4.5 cm. wide, situated between and around the seminal vesicles. It was impossible to treat the new growth effectively, and it increased rapidly in size. The patient died two months after his admission to the hospital. Autopsy disclosed lymphosarcoma of the prostate gland.

Since these publications of Symmers and Ferguson and Stewart, other cases of lymphosarcoma of the prostate gland have been reported. Of these, those reported by Mason,⁶ Cole and Martin,⁷ Rathbun and deVeer⁸ and Smith⁹ have all been cases which we believe can be accepted as cases of definite prostatic lymphosarcoma. Some of the tumors occurred in patients much older than those of Symmers and Ferguson and Stewart. Cole and Martin's patient, for example, was a 56 year old man and Rathbun and deVeer's a man of 52. The duration of the disease seemed to vary between three and nine months. In all reported cases the growth was a rapidly progressing one, infiltrating diffusely the surrounding structures and producing widespread lymphatic metastases. In all cases the growth was fatal despite a variety of therapeutic measures.

Another case, although not one of a malignant tumor, might be included in this series, particularly because of its peculiar histologic aspect. The tumor occurred in a 68 year old man and was diagnosed as lymphoma of the prostate gland. The case was reported by Wegelin.¹⁰

The patient had an indefinite history of gastrointestinal disorders with marked prostatic hypertrophy of two months' duration. The prostate gland was found to be of the size of an apple, and cystoscopic examination showed it to protrude markedly into the bladder. Perineal prostatectomy was done, and an encapsulated tumor measuring 5.5 by 4.5 by 3 cm. and weighing between 50 and 60 Gm. was removed from the right side of the gland. The left lobe of the prostate appeared perfectly normal. After initial improvement septicemia suddenly developed, and the man died twenty days after the operation. No autopsy was done.

Histologically, the neoplasm was found to consist for the greater part of fully mature, round, follicle-like lymphatic tissue, the follicles ranging from 0.5 to 1.5 mm. in diameter. Often these follicles were closely packed and formed large conglomerates of lymphatic cells. Germinal centers were absent. The lymphatic tissue was indistinctly separated from the ground substance of the tumor, which consisted of smooth muscle tissue. The muscle tissue throughout the entire tumor was diffusely infiltrated with lymphocytes. The lack of glandular tissue in the neoplasm and the appearance of the encapsulated muscle fibers led Wegelin to diagnose lymphoma arising in an encapsulated myoma of the prostate gland.

6. Mason, D. G.: Primary Malignant Lymphocytoma of the Prostate Gland, *Arch. Path.* **16**:803-808 (Dec.) 1933.

7. Cole, F. H., and Martin, L. R.: Lymphosarcoma of the Prostate, *J. Urol.* **31**:803-811, 1934.

8. Rathbun, N. P., and deVeer, J. A.: Lymphosarcoma of the Prostate, *J. Mt. Sinai Hosp.* **4**:771-780, 1938.

9. Smith, L. D.: Lymphosarcoma of the Prostate, *J. Urol.* **38**:375-382, 1937.

10. Wegelin, C.: Ueber ein Lymphom der Prostata, *Wien. klin. Wchnschr.* **48**:1236-1237, 1935.

Recently we have had an opportunity in this laboratory to study a case of lymphosarcoma of the prostate gland. This case is now reported in detail.

REPORT OF A CASE

A man 62 years old was admitted to a hospital on May 9, 1939, complaining of burning urination for the previous two or three years and of frequency of urination and nocturia for seven weeks. Pain low in the abdomen accompanied urination. His last normal micturition had occurred two days previously. Since then he had urinated by dribbling only. Except for chronic constipation his past history was not pertinent. On physical examination the lower part of the abdomen was tender and the bladder distended. Rectal investigation revealed a hard, enlarged and tender prostate gland. The urine at this time contained albumin (2+), many red blood cells and neutrophils. The erythrocyte and leukocyte counts were within normal limits. The blood chemical findings were reported as within normal range. The Wassermann test was negative.

On May 15 suprapubic prostatectomy, cystotomy and bilateral vasectomy were done. The material submitted for examination consisted of several irregular pieces of firm grayish white tissue. The amount received indicated that the gland was moderately enlarged. On histologic examination the organ was found to be diffusely invaded by a new growth, which was considered to be lymphoblastoma. Six days after the operation pneumonia developed, but the patient recovered and was discharged on June 10, at which date the suprapubic wound was entirely healed. No urinary difficulties were noticed.

On July 2, approximately seven weeks after the first operation, the patient again appeared complaining of severe pains in the bladder region, especially about the operative scar. Between the time of his first admission to a hospital and this date, he had had about 10 treatments with roentgen rays of high voltage. Examination now revealed a hard, large, irregular mass in the region of the bladder. Inguinal lymph nodes, however, were not palpable.

The patient was transferred to the Albany Hospital on July 24. At this time a large hard tumor, lying directly beneath the skin above the symphysis pubis in the midabdominal line, was noted. The lower end of the suprapubic scar of the previous operation was ulcerated and contained a sinus, through which urine leaked. There were also small pink nodules in the suprapubic wound. On rectal examination an extremely large prostatic tumor, beyond which the exploring finger could not be passed, was found. At this time the inguinal lymph nodes were greatly enlarged, some measuring 3 cm. in length. The next day suprapubic irrigation of the bladder was performed. This procedure was painful and yielded a large amount of purulent material.

The same day biopsy of the subcutaneous tumor showed extensive diffuse infiltration of the stratum corium and the stratum subcutaneum by a rapidly growing, highly malignant, widely infiltrating neoplasm. In general the cells which formed the new growth were quite uniform in size. They appeared approximately round or oval, sometimes polyhedral, and contained scanty, finely granular, faintly basophilic cytoplasm with extremely faint cell membranes. The nuclei were large, vesicular, irregularly round or oval, had distinct nuclear membranes and contained small numbers of minute, deeply stained chromatin granules which stood out sharply in a finely reticulated pale blue nucleoplasm. Mitotic figures in all phases were present in abundance. Giant and multinucleated cells were not observed.

The arrangement of the neoplastic cells was worthy of note. Usually they formed chainlike strands from one to several cells thick, which infiltrated and separated the collagenous strands of the subepithelial tissues. One gained the impression that this chainlike or cordlike arrangement was not the result of an inherent tendency on the part of the cells to grow in this fashion but rather the result of the invasion of natural tissue planes. Often the cells in any given strandlike mass overlapped, seeming to form elongated and distinct entities.

Sometimes, especially when the tumor invaded the looser tissues of the stratum subcutaneum, the chainlike or cordlike arrangement of the cells was less frequently



Fig. 1.—The entire tumor mass involving the skin and the bladder. X indicates the bladder; XX, the deferent ducts. For detailed description see the text.

noted. Here the neoplastic growth was more diffuse, and the individual cells appeared quite closely packed together, being separated only occasionally by delicate strands of collagen fibrils. These fibrils were considered to be part of the preexistent stroma.

In one section lymphatics of the subepithelial portion of the stratum corium were dilated and contained neoplastic cells. Here the cells appeared as separate entities, often closely packed, but sometimes occurring singly. Under these conditions the cytoplasm was more readily seen and the nucleus appeared even more vesicular than elsewhere. The cells sometimes resembled atypical monocytes.

Moderate numbers of tumor cells showed degenerative changes, which varied from early pyknosis and karyorrhexis to complete disintegration of some cells. Occasional eosinophils were found within the tumor tissue.

On the basis of these observations a diagnosis of lymphoblastoma was made by a member of this department. In view of the fact that intensive treatment with high voltage roentgen rays failed not only to affect the tumor but even to prevent further growth and enlargement, the sections were reexamined by one of us (A. W. W.). It was felt that in spite of the anaplastic lymphoblastomatous character of the growth the cells in some situations appeared more like epithelial cells than like lymphoblasts. Indeed, the cordlike arrangement, which in some places was pronounced, the occasional tendency of some of the cells to form crude alveolus-like structures and the clinical history of primary prostatic origin led to the conclusion that the new growth was a highly anaplastic, radioresistant carcinoma of prostatic origin. As such the new growth was reported to the tumor clinic.

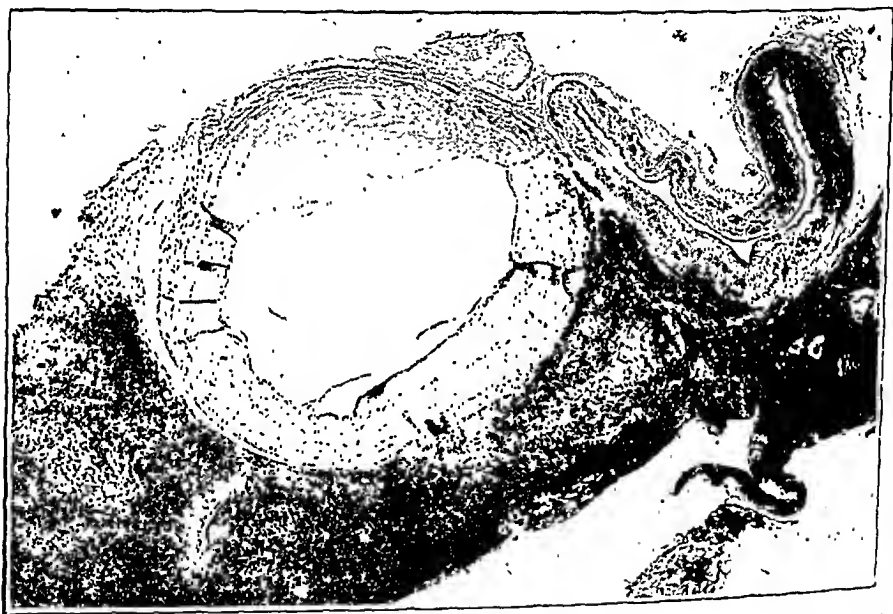


Fig. 2.—Low power view of right hypogastric artery and vein surrounded partially by tumor tissue.

The urine at this time was cloudy, with a specific gravity of 1.020 and with a neutral reaction; it contained albumin (2+) but no sugar. Great numbers of pus cells were present. The erythrocyte count was 3,400,000, with hemoglobin 74 per cent of normal. There were 9,700 leukocytes per cubic millimeter, with 81 per cent neutrophils, 1 per cent eosinophils, 10 per cent lymphocytes and 6 per cent monocytes. The blood sugar was 84.7 mg. per hundred cubic centimeters; the nonprotein nitrogen, 31.4 mg., and creatinine, 1.15 mg. The temperature varied between 98 and 101 F.

On July 27 roentgenograms of the pelvis did not show any bone metastases. On August 4 the entire skeleton was examined roentgenographically and no evidence of tumor involvement could be found. The lungs also were free from metastases. On July 29 treatment with roentgen rays of high voltage was again

begun, but the growth increased in size in spite of intensive doses given over the right and left anterior and posterior lower abdominal quadrants. On August 28 the patient died.

Autopsy.—The body of this patient was well developed but poorly nourished. A bulging tumor was present beneath a partly healed midabdominal surgical incision. Its entire central portion was soft and necrotic and formed a cavity, in which a rubber drain was found. This tumor was extremely hard and was intimately connected with the overlying skin and the scar. It appeared to penetrate deeply into the abdominal cavity and also into the skin and subcutaneous

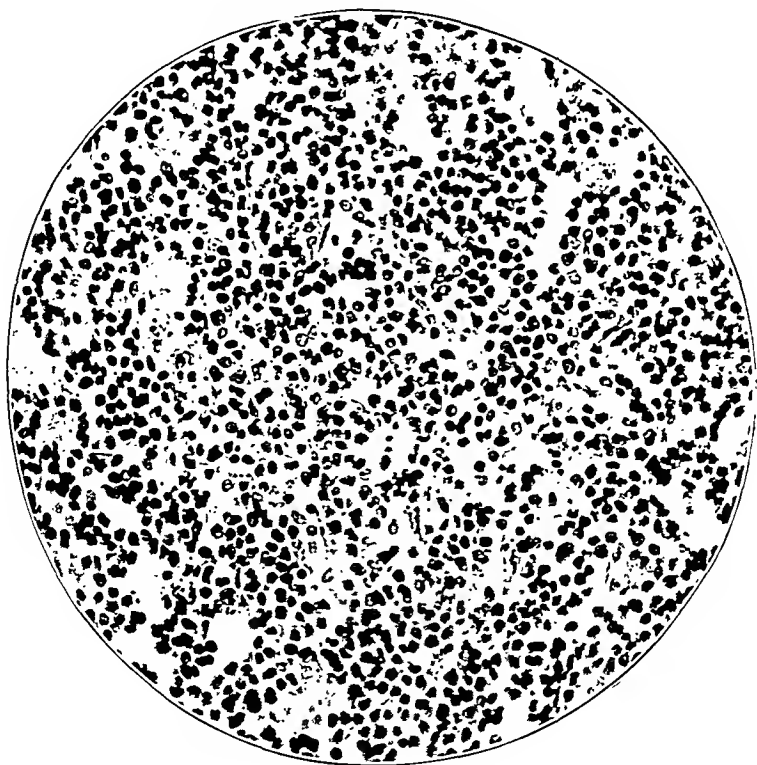


Fig. 3.—Low power view of tumor tissue from prostate gland.

tissues over the symphysis pubis. Several hard inguinal lymph nodes were felt on palpation.

When the peritoneal cavity was opened, an extremely large tumor was found occupying the entire pelvis. This mass extended to about 5 cm. above the umbilicus. The omentum, very poor in fat, was drawn upward, leaving the intestinal loops uncovered. The liver edge extended about 6 cm. below the costal margin. The serosa of the intestinal loops was covered by a fibrinous exudate, which glued adjacent coils lightly together. There was a small amount of a purulent exudate in the dependent part of the cavity. The mesentery was studded with small and large metastatic nodules. Along the entire course of the abdominal portion of the aorta were large, hard lymph nodes, many of them matted together.

The pelvic tumor mass with the overlying skin and scar and all organs attached to or buried within it was carefully mobilized and taken out en bloc. This mass measured 22 cm. in length, 17 cm. in width and about 17 cm. in thickness (fig. 1). On section the cut surfaces were yellowish white and very hard. In the center, however, and in places extending to the surface, the mass was discolored and showed extensive necrosis and softening. No evidence of prostatic tissue could be found, which may be explained on the basis of the previous prostatectomy. The bladder, which overlay the growth, appeared necrotic, and its mucosa was covered by a dirty, dark grayish brown material, which could be scraped off easily with a knife. Extending from the outer wound into the bladder cavity there was an inflamed sinus tract, which measured about 1.5 cm. in width. The old scar and the wound were diffusely infiltrated by tumor tissue, and sections through the

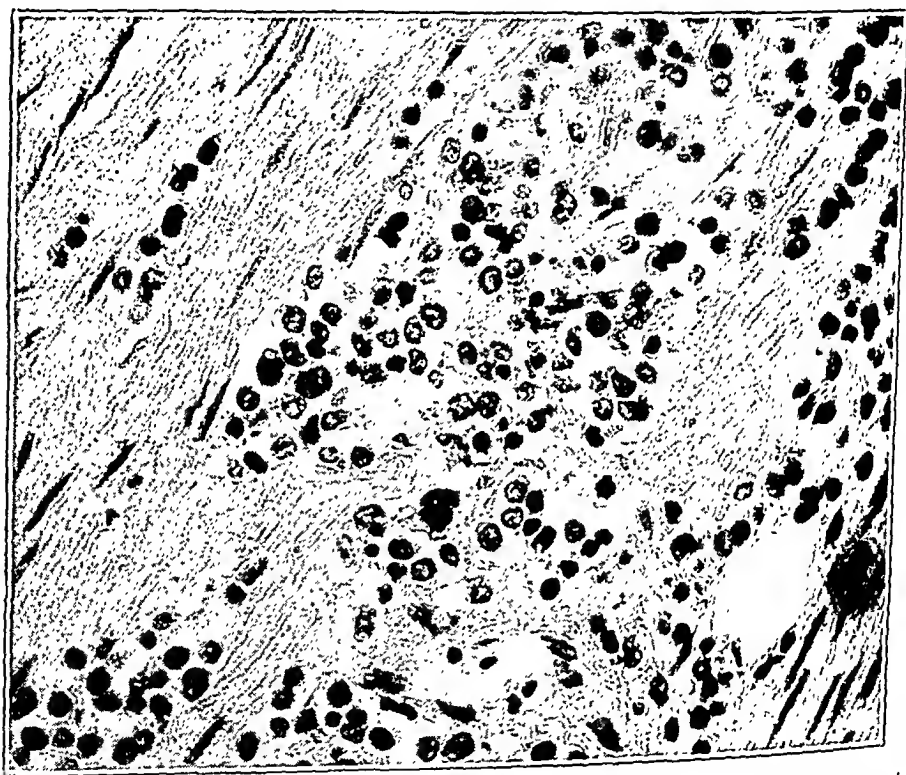


Fig. 4.—High power view of tumor tissue infiltrating the rectus abdominis muscle. Note the occasional appearance of multinucleated tumor cells.

deferent ducts and the ureters showed these structures to be completely embedded in neoplastic tissue. The new growth also had invaded the symphysis pubis.

Except for the incarceration within the pelvic tumor of the sigmoid colon and retroceally situated appendix, the gastrointestinal tract did not disclose any tumor involvement.

The lungs, except for several circumscribed tumor nodules near the pleura, were not unusual.

The pancreas weighed 115 Gm. and was rather hard to palpation. It cut with increased resistance and was surrounded by several large, hard nodules of grayish white appearance, apparently lymph nodes, infiltrated by metastases. The adrenal glands were not remarkable except for the fact that they were surrounded by firm tumor tissue.

The kidneys were surrounded by thick, hard, nodular capsules, which on section were grayish white and neoplastic. The right kidney weighed 185 Gm.; the left, 250 Gm. When the thickened capsules were removed, numerous small cortical abscesses filled with creamy pus projected from the surface of each organ. Grossly it could not be determined definitely whether or not any tumor metastases were present. The pelvis were markedly dilated and contained a thick purulent exudate. Their mucous surfaces were markedly congested and inflamed. Both ureters were dilated and their lumens filled with pus. In some places their walls averaged 0.1 cm. in thickness. Their inferior portions disappeared in the tumor mass. On the right side the hypogastric artery entered the tumor mass and was lost completely for part of its course. It emerged again about 1 cm. above the inguinal canal. On the left side tumor tissue lay close to, but

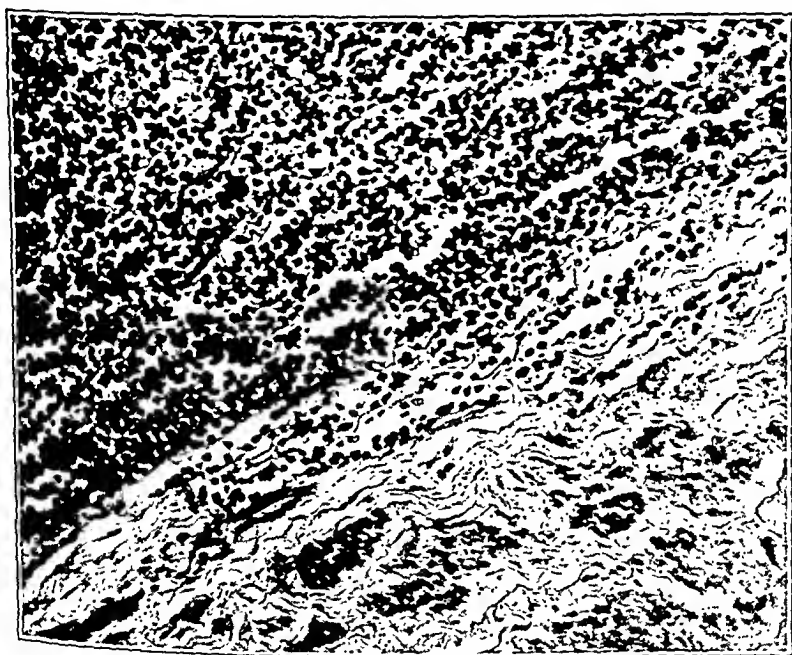


Fig. 5.—Low power view of tumor tissue infiltrating the adventitia of the right hypogastric artery.

did not surround or invade, the hypogastric artery. Both deferent ducts were embedded in neoplastic tissue, but they also emerged again from the tumor to enter in normal fashion into the scrotal sac. The skin above and directly below the symphysis pubis contained several metastatic nodules. None were seen in the skin of the scrotum or the penis.

Microscopic Examination.—Sections from different viable portions of the large pelvic tumor showed it to be histologically a homogeneous new growth composed of small, irregularly rounded, undifferentiated cells which formed no structure, assumed no characteristic arrangements and appeared as discrete entities. In general the cells resembled lymphocytes or cells of the lymphocytic series (fig. 3). The type cell was small, irregularly round or oval, with a minute amount of faintly staining, slightly acidophilic cytoplasm and a round or ovoid nucleus, which

was almost as large as the cell itself. The nucleus tended to be hyperchromatic with a distinct nuclear membrane and contained a moderate amount of deeply staining, finely granular chromatin. While the majority of the neoplastic cells were small, measuring from 6 to 8 microns in diameter, moderate numbers of them were quite large, some being 12 microns wide. Occasionally multinucleate giant cells were found (fig. 4). Many of the cells were actively growing, as indicated by the presence of mitotic figures in all phases. The neoplasm infiltrated all tissues widely. In the rectum the serosal surface was extensively infiltrated, and in some sections the new growth penetrated the two smooth muscle layers and invaded the submucosa and even the mucosa. In the sigmoid colon, neoplastic invasion of the serosa and muscularis was marked, but the submucosa and mucosa were not involved. The periappendical fat was likewise infiltrated, and in some

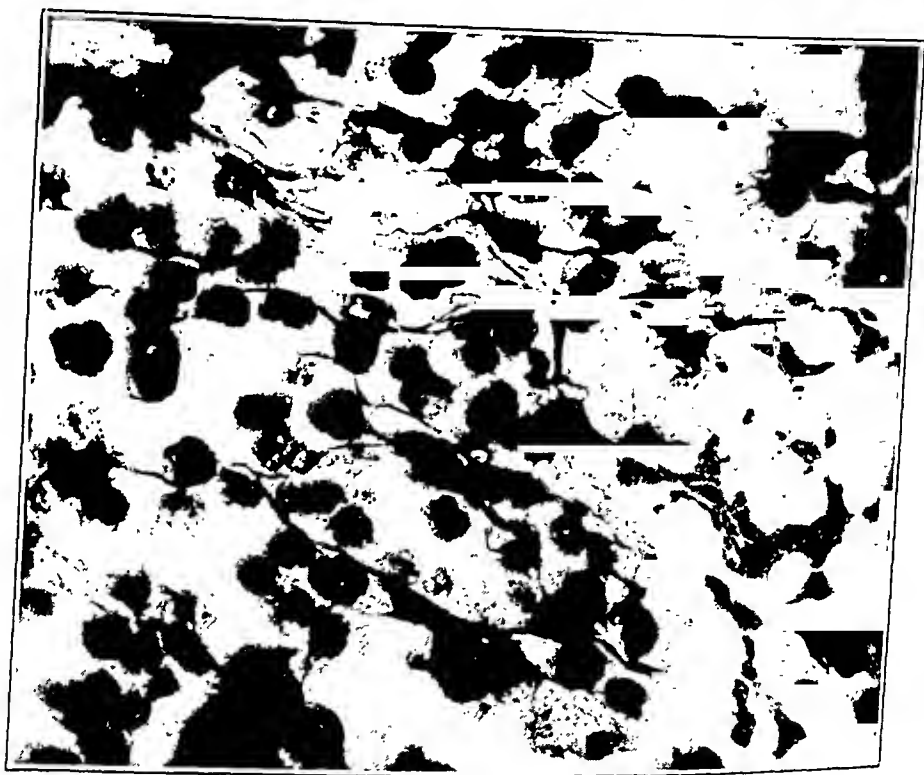


Fig. 6.—Silver preparation of tumor tissue, showing the abundant fine reticulum.

situations even the muscularis was invaded. The adventitia of the hypogastric arteries, particularly that of the right, was diffusely infiltrated (figs. 2 and 5), and the walls of the ureters and the deferent ducts showed invasion which in some situations extended as deep as the epithelial linings of their lumens. Even in the anterior abdominal wall there was extensive infiltration of all tissues from subperitoneal fat through the strands of the rectus muscle into the skin and subcutaneous tissue. In the latter situation the neoplastic cells resembled lymphocytes much more definitely than did the tumor cells in the pelvic mass (fig. 4).

In many situations the neoplastic tissue showed degenerative changes which varied from pyknosis and karyorrhexis with granular or hyaline degeneration of the cytoplasm to necrosis and the disappearance of great numbers of tumor cells, with resulting softening and liquefaction of the growth. It is probable that these changes were due, in part at least, to intensive irradiation.

Sections from the bladder wall showed extensive infiltration of the muscle up to the edematous, chronically inflamed mucous membrane. In the specimens examined the mucosa was not involved, however.

Where the neoplasm invaded fat tissue, large vacuolated cells with vesicular nuclei were often mixed with the tumor cells. Sometimes these cells also contained dark-staining granular nuclear material. They were interpreted as macrophages containing fat and granular material from disintegrated tissue. In some situations lymph channels and possibly even small blood vessels were found to contain typical tumor cells.

A section of a part of the new growth which infiltrated fat was stained by the method of Foot and Foot for the demonstration of reticulin fibrils. Throughout the entire metastatic growth delicate reticulin fibrils were present between the tumor cells. They were considered to have been formed by the tumor cells (fig. 6). Sections from many of the metastases were also examined. In all situations, notably in the pancreas, in the perirenal and periadrenal fat and in the lungs and pleurae, the histologic and cytologic characters of the growth were similar to those already described, except for the fact that, if anything, the tumor cells even more closely resembled lymphocytes and lymphoblasts than did the cells of the primary tumor. The final pathologic diagnosis was: lymphosarcoma, reticulum cell type, of the prostate gland with extensive invasion of the surrounding tissues and widespread generalized metastases to aortic abdominal, peripancreatic and mesenteric lymph nodes, lungs and pancreas.

COMMENT

Evaluation of the reported cases of lymphosarcoma of the prostate gland is difficult, since no definite and accepted criteria for the classification of the various prostatic malignant tumors have been established. Attempts at classification have been made by various investigators (Proust and Vian¹¹; Smith and Torgerson¹²; Randall and Boland¹³; Costa¹⁴; Lowsley and Kimball¹⁵) but unanimity of opinion is far from complete even in these careful critiques. It is particularly in the cases of sarcoma, small round cell sarcoma, lymphosarcoma and anaplastic carcinoma of the prostate gland that classification appears to be most difficult. We do not wish at this time to discuss prostatic tumors in general but rather to consider only the lymphosarcoma in the light of the observations made by others as well as by ourselves.

11. Proust, R., and Vian, E.: Le sarcome de la prostate, *Ann. d. mal. d. org. g nito-urin.* **25**:721-778, 1907.

12. Smith, R. R., and Torgerson, W. R.: Sarcoma of the Prostate, *Surg., Gynec. & Obst.* **43**:328-337, 1926.

13. Randall, A., and Boland, H.: A Critique of Prostatic Sarcoma, *Tr. Am. A. Genito-Urin. Surgeons* **22**:245-260, 1929.

14. Costa, A.: Malignit  e trasformazione maligna del mioma (leiomioma maligno della prostata), *Tumori* **14**:115-142, 1928.

15. Lowsley, O. S., and Kimball, F. N.: Sarcoma of the Prostate, with a Review of the Literature, *Brit. J. Urol.* **6**:328-348, 1934.

In the opinion of Ewing,¹⁶ even the possibility of lymphosarcoma ever occurring in the prostate gland should be seriously questioned. He argued that the architecture of this gland does not favor the development of lymphosarcoma. This view, however, appeared too skeptical to Wegelin, and Symmers pointed out that the prostate gland belongs to the so-called auxiliary lymphoid systems, with the adrenal glands, lungs, liver, kidneys, testes and other organs. He expressed the belief that the gland normally contains interstitial lymphoid foci, which under ordinary circumstances are likely to be overlooked but which in certain cases of disease may be readily identified. He concludes that there is no apparent reason why a tumor of lymphoid cells should not spring from such a focus in the prostate. In a recent personal interview with one of us, Dr. Ewing admitted the possibility of a lymphatic tumor in the prostatic gland.

Thus even the possibility of primary prostatic lymphosarcoma is controversial. Actual studies of prostate glands to demonstrate the presence of lymphoid tissue occurring normally or to trace its development in disease of the organ are rare. Most of those which have been made were carried out on experimental animals, particularly dogs. In 1900 Walker¹⁷ found lymphoid tissue in human and animal prostate glands. Shortly thereafter Weski¹⁸ reported a study of an island of lymphoid tissue in a dog's prostate, an occurrence previously noted by Waldeyer. He regarded this finding as pathologic, although no other evidence of any disease could be found in the animal. Later he demonstrated lymph nodules in 2 human prostate glands and pointed out that they were normal structures. Similar observations were made by Deaver¹⁹ and by Wilson and McGrath.²⁰ More recently Fukase²¹ studied 222 prostates obtained at operations and autopsies and found that small, primitive or rudimentary lymph nodes occur normally throughout the gland in the form of small aggregations of lymphocytes, located beneath the glandular and duct epithelium, particularly toward

16. Ewing, J.: *Neoplastic Diseases*, ed. 4, Philadelphia, W. B. Saunders Company, 1940, p. 852.

17. Walker, G.: *A Contribution to the Study of the Anatomy and Physiology of the Prostate Gland, and a Few Observations on the Phenomenon of Ejaculation*. Bull. Johns Hopkins Hosp. **11**:242-256, 1900.

18. Weski, O., abstracted, *Jahreshb. ii. d. Fortschr. d. Anat. u. Entwicklungsgesch.*, 1899, Anat. Abteilung 1-10; cited by Walker.¹⁷

19. Deaver, J. B.: *Enlargement of the Prostate*, Philadelphia, P. Blakiston's Son & Co., 1905, p. 36.

20. Wilson, L. B., and McGrath, B. F.: *Surgical Pathology of the Prostate*, Surg., Gynec. & Obst. **13**:647-681, 1911.

21. Fukase, N.: *Hyperplasia of the Rudimentary Lymph Nodes of the Prostate*, Surg., Gynec. & Obst. **35**:131-136, 1922.

the outlets of the ducts. He considered them to be analogous to the rudimentary lymph nodes found in other organs, such as the liver, kidneys and uterus.

Fukase also went so far as to differentiate between normal rudimentary lymph nodes, hyperplastic nodes and inflammatory infiltration. The normal rudimentary lymph nodes were found in all normal adult human prostate glands and consisted of small aggregations of small lymphocytes, slightly more crowded at the periphery than at the center, but not possessing any well defined germinal centers. They could not be seen with the naked eye in stained sections. The hyperplastic nodes varied in size from 0.15 mm. to 0.5 mm. or larger, so that they could be seen with the naked eye in stained preparations. Well defined germinal centers were found in the largest ones. The inflammatory infiltrations were "readily" distinguished from the rudimentary lymph nodes by the uniform character of the cells, the arrangement of these cells, the demonstration of the endothelium of the lymphatic vessels and the fibrils of the reticulum.

It was Fukase's belief that hyperplasia of these rudimentary lymph nodes of the prostate gland occurred chiefly in chronic hyperplastic prostatitis and carcinoma.

Also Wegelin felt that while lymphatic tissue is probably normally not present in the prostate gland, as a result of chronic inflammation with destruction of muscle tissue and overgrowth of connective tissue accompanying hypertrophy, true lymph follicles with germinal centers may definitely develop.

In our own experience lymphoid tissue with and without germinal centers is frequently seen in prostate glands. In the absence of any systematic study of this controversial subject on our part we are not qualified to substantiate Fukase's and Wegelin's observations. However, the foregoing observations led to the suggestion by Ferguson and Stewart that lymphosarcoma may originate from lymphoid tissue which arises as a result of old past inflammation of the genitourinary tract, such as gonorrhea, a supposition also adopted by Rathbun and deVeer. In our patient's case, no such history of past inflammation could be elicited, so that here the question must remain unanswered.

The question as to whether or not these tumors, including our own, are really lymphosarcoma and not highly anaplastic carcinoma—the most frequent type of malignant neoplasm of the prostate gland—must perforce be raised. In part this has already been discussed. Although we feel that Quinby's case, for example, can be accepted as one of primary prostatic lymphosarcoma, Randall and Boland pointed out that the tumor presented a number of features "not so infrequently seen" in prostatic carcinoma. Indeed in our own case a diagnosis of anaplastic

carcinoma was made by one of us (A. W. W.) on the second biopsy. Sections of this tissue showed atypical, anaplastic cells which tended at times to grow in groups or masses much as undifferentiated cells of carcinoma would. It must be borne in mind, however, that this biopsy included only a minute portion of a large tumor, which in different parts presumably showed different features. The multiple tumor sections examined post mortem, however, leave no doubt that we are dealing here with lymphosarcoma, not carcinoma. It is also noteworthy that there were no bone or lung metastases, so characteristic of primary prostatic carcinoma. In this case the spread appeared to be purely lymphatic or by direct extension.

Although we do not wish to emphasize too strongly the presence of multiple and readily visible reticulum fibrils, seen in silver preparations, as supporting the diagnosis of lymphosarcoma, we feel that their presence at least speaks against a diagnosis of carcinoma.

Whether, finally, the new growth originated really in the prostate gland and not in the urinary bladder, from which it invaded the prostate gland secondarily, is a matter of conjecture. Since both organs were widely involved and the prostate itself was actually unrecognizable at the time of autopsy, it would appear difficult to state with certainty from postmortem study alone that the growth originated in the prostate gland. However, from the clinical investigations in this case we feel sure that the tumor originated in that organ. Also from the frequent observations of lymphatic tissue in prostate glands examined in this laboratory we feel that the possibility of the development of lymphosarcoma is not remote.

Of great interest in this patient was the fact that the tumor proved to be extremely radioresistant, even growing rapidly larger during and after intensive treatment with roentgen rays of high voltage. This of course is not a definite point of differentiation between lymphosarcoma and anaplastic carcinoma, particularly since lymphosarcoma in general is quite radiosensitive and this growth was certainly not. Nevertheless the present case as far as we can determine is the fourth one in which prostatic lymphosarcoma received extensive high voltage roentgen irradiation without benefit.

SUMMARY

Lymphosarcoma of the prostate gland is a rapidly growing neoplasm which infiltrates the surrounding tissues diffusely, produces widespread metastases and proves fatal in from three to nine months. It may occur in any age period but appears more frequently in early adult life. Its causes are somewhat obscure, but it may arise from the preexisting lymphatic tissue in the gland or from the hyperplastic lymphoid tissue formed as a result of chronic inflammation (compare sarcoma in Hodg-

kin's disease). Radiation therapy appears to be without any beneficial effect in the treatment of lymphosarcoma of the prostate gland; in fact, it may enhance the growth of the tumor. In establishing the diagnosis of lymphosarcoma of the prostate gland extreme care must be taken to scrutinize all clinical, therapeutic, gross anatomic and histologic characteristics of the new growth in order to avoid confusion with highly anaplastic carcinoma, the most frequent type of malignant tumor of this organ.

Dr. John E. Heslin gave us permission to make use of the clinical data in the case reported.

ANTERIOR RESECTION FOR CANCER OF THE RECTOSIGMOID

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It is well established that abdominoperineal resection in one or more stages is the operation of choice for cancer of the rectum. Less extensive procedures are justifiable only when the radical operation is specifically contraindicated. However, when one is dealing with cancer of the rectosigmoid, the situation is less clear, for it is possible that in selected cases anterior resection of the rectum followed either by anastomosis or by closure of the rectal stump with permanent colostomy may prove equally satisfactory. Anterior resection offers hope of avoiding permanent colostomy and since it is a less extensive procedure, should have a lower operative mortality.

The rectosigmoid is that portion of the large intestine in which the narrow sigmoid colon undergoes a gradual enlargement before joining the rectum. Its exact position is variable. By some it has been estimated to be about 2 inches (5 cm.) above the superior valve of Houston. Others place it as lying opposite the third sacral vertebra. For the purpose of this discussion it may be described as that portion of the pelvic colon in which a neoplasm cannot be delivered sufficiently high to permit a satisfactory end to end anastomosis or Mikulicz resection and yet is not in the ampulla of the rectum. The frequency of malignant lesions in this area is not inconsiderable. Pemberton and Dixon¹ found that 17 per cent of over 3,000 cancers of the colon and the rectum were in the rectosigmoid. Of the 270 patients with cancer of the colon and the rectum admitted to the Peter Bent Brigham Hospital during the five year period covered by this study (1934 to 1939), 24 had the lesion in the rectosigmoid.

There are several anatomic and pathologic factors which make neoplasms in this area worthy of especial consideration. At this point the mesosigmoid becomes shortened, and just below this area it disappears entirely, leaving the bowel with a peritoneal covering on the anterior side only. The blood supply comes from the terminal branches of the

From the Surgical Clinic of the Peter Bent Brigham Hospital.

1. Pemberton, J. de J., and Dixon, C. F.: Summary of End-Results of Treatment of Malignancy of Thyroid Gland and Colon, Including Rectum and Anus, Surg., Gynec. & Obst. 58:462 (Feb., no. 2A) 1934.

superior hemorrhoidal artery, and an adequate resection of the possible areas of lymphatic extension necessitates destroying this vessel. Thus the vascular supply to the resected ends of the bowel must be supplied by the variable and inconstant middle hemorrhoidal arteries and the marginal branch of the sigmoidal arteries. Finally, there is the possibility that cancer of the rectosigmoid may extend to the lymphatics below the point of resection, that is, to the tissues about the rectum proper. For these various reasons many surgeons feel that an abdominoperineal resection is the operation of choice for lesions in this area.² In recent years, however, there has been a revival of interest in segmental resection of the pelvic colon.³ In general, the reports of the surgeons using this type of resection have been favorable. In this paper the more recent experiences at the Peter Bent Brigham Hospital are recorded.

ANALYSIS OF CASES

During the period 1934 to 1938, inclusive, 24 patients with cancer of the rectosigmoid were cared for in the Peter Bent Brigham Hospital. In 3 instances no operation was performed because of evident extensive metastases. In 6 cases an exploratory laparotomy followed by colostomy was done. There were 2 postoperative deaths. None of the patients survived more than one year after operation. In 15 cases the lesion was considered operable; 7 of the patients were treated by abdominoperineal resection, and 8 were treated by anterior resection, followed in 2 instances by an immediate end to end anastomosis. The operative mortality, survival periods and pathologic gradings in these 15 cases are detailed in the table. The series is too small to permit of statistical evaluation, but several observations are worthy of note. There were 2 deaths in the group of patients operated on by abdominoperineal resection. There were no deaths among the patients on whom anterior resection was performed. Four of the 5 patients operated on by the abdominoperineal route were alive and well without evident recurrence at the time of the last follow-up visit; 6 of the 8 patients surviving anterior resection were well without recurrence at the time of writing. There is a close correlation between the pathologic grading of the lesions and recurrence. To date there has been no recurrence among those patients graded A or B. It is unfortunate that in both the patients on whom anastomosis was performed, the lesion was extensive.

2. Rankin, F. W., and Graham, A. S.: *Cancer of the Colon and Rectum*, Springfield, Ill., Charles C. Thomas, Publisher, 1939.

3. Horsley, J. S.: Resection of the Rectosigmoid and Upper Rectum for Cancer, with End-to-End Union, *Surg., Gynec. & Obst.* **64**:313 (Feb., no. 2A) 1937.
Dixon, C. F.: Surgical Removal of Lesions Occurring in the Sigmoid and Rectosigmoid, *Am. J. Surg.* **46**:12 (Oct.) 1939.

Two of the cases in which anterior resection was performed (cases 9 and 10) will be discussed in more detail because they illustrate a particular application of this type of operation which has not been given due consideration.

CASE 9.—The patient was a 39 year old woman who first entered the Peter Bent Brigham Hospital in the summer of 1936 with acute obstruction of the large bowel due to a malignant growth in the sigmoid. A preliminary colostomy was done followed by a resection of the tumor with an end to end anastomosis; after this the colostomy opening was closed. The growth was adenocarcinoma, growing fairly rapidly, with numerous lymph node metastases. The patient was well for the next eighteen months. At the end of that time, however, she reentered the hospital because of profuse bleeding from the rectum. Examination showed her

Operative Mortality, Survival Periods and Pathologic Gradings in Fifteen Cases of Cancer of the Rectosigmoid

Case	Operation	Operative Death	Survival Period at Time of Last Follow-Up	Pathologic Grading *
1	Abdominoperineal resection	0	1.2 years; dead	C3
2	Abdominoperineal resection	0	3 years	A2
3	Abdominoperineal resection	0	5 years	A2
4	Abdominoperineal resection	+	0	A2
5	Abdominoperineal resection	+	0	B2
6	Abdominoperineal resection	0	2 years	A2
7	Abdominoperineal resection	0	3 years	B2
8	Anterior resection	0	2 years	B2
9	Anterior resection	0	4 years	C2
10	Two stage anterior resection †	0	2 years	B2
11	Anterior resection with anastomosis	0	6 months; dead	C3
12	Anterior resection	0	2 years	B2
13	Anterior resection	0	8 months; dead	C3
14	Anterior resection	0	2 years	A1
15	Anterior resection	0	1 year	B2

* The method of classification is essentially that of C. E. Dukes (Classification of Cancer of the Rectum, J. Path. & Bact. 35:323 [May] 1932). Grade A indicates that the lesion is confined to the bowel wall; grade B means local extension; grade C indicates metastasis to lymph nodes. The figures 1, 2 and 3 refer to the rate of growth of the tumor as estimated microscopically: 1 indicates slow growth; 2, intermediate growth; 3, rapid growth.

† See text for details.

to be in good general health, but a large fixed mass was palpable in the left lower quadrant of the abdomen. By a roentgen examination after she had been given a barium sulfate enema and sigmoidoscopy together with biopsy adenocarcinoma was demonstrated at the site of the previous resection. Here, then, was a young woman with an early recurrence of a rapidly growing sigmoid neoplasm with proved metastasis to lymph nodes. Was an exploratory operation justifiable? It is my feeling that unless distant metastases can be demonstrated, a patient with recurrent neoplasm of the colon should be submitted to an exploratory procedure even though clinically the growth seems of doubtful operability.

A second operation was performed and an extensive tumor mass observed just below the brim of the pelvis. It was adherent to the lateral parietes, the left adnexa and the broad ligament. Extensive resection was performed, and the remainder of the sigmoid and the pelvic colon down to the upper part of the rectum were removed. The left ovary and the broad ligament were included in the resection. The rectal stump was inverted but left above the pelvic floor. Except

for an iliac abscess which required drainage, the postoperative course was uneventful. This patient was alive and well, without evidence of recurrence at the time of writing, four years after the operation.

In this instance an anterior resection was performed to extend the scope of resection of a tumor of the lower part of the sigmoid. A less extensive operation with another anastomosis above the pelvis might have been performed, but in view of the initial recurrence of the growth it was thought that radical resection with the acceptance of a colostomy was the preferable procedure. The use of anterior resection under such circumstances has not been given due consideration. The possibility of



Fig. 1.—Roentgenogram showing two constricting lesions of the colon, one in the descending portion and the other in the lower part of the sigmoid.

avoiding colostomy in this type of resection by an anastomosis in the hollow of the sacrum will be discussed later.

CASE 10.—A 54 year old woman entered the hospital because of fever, chills and pain in the left lower part of the abdomen. Physical examination disclosed a large, easily palpable, acutely tender mass in the left lower quadrant of the abdomen and the left vault of the vagina. Roentgen examination after the administration of a barium sulfate enema showed two rather extensive areas of narrowing of the large bowel, one in the lower part of the sigmoid and one in the midportion of the descending colon (fig. 1). After a period of ten days of preparation, during which the white blood cell count and the temperature became normal and the

pelvic mass decreased in size, operation was performed. There were two separate neoplasms, one in the descending colon—a long constricting lesion without evident local extension or metastases—and a larger rounded lesion, about 15 cm. in diameter, in the lower part of the sigmoid. The latter lesion was adherent to several loops of small bowel, to the bladder and to the left lateral wall of the abdomen. Although there were considerable edema and inflammation in the lower lesion, operability appeared doubtful. However, without distant metastases the operability of sigmoidal or rectal lesions is exceedingly difficult to evaluate in the presence of any degree of inflammation. Diversion of the fecal stream must be done and a reevaluation of the tumor made after a period of ten days to three weeks. Accordingly, the splenic flexure was demounted and the proximal lesion resected. The transverse colon was then brought through the upper portion of the left rectus incision as a permanent colostomy, and the lower loop of the bowel was brought through the opposite end of the wound as a distal colostomy. The omentum was attached along the mesentery of the lower loop of the bowel in an effort to exclude this area as much as possible from the rest of the abdomen.

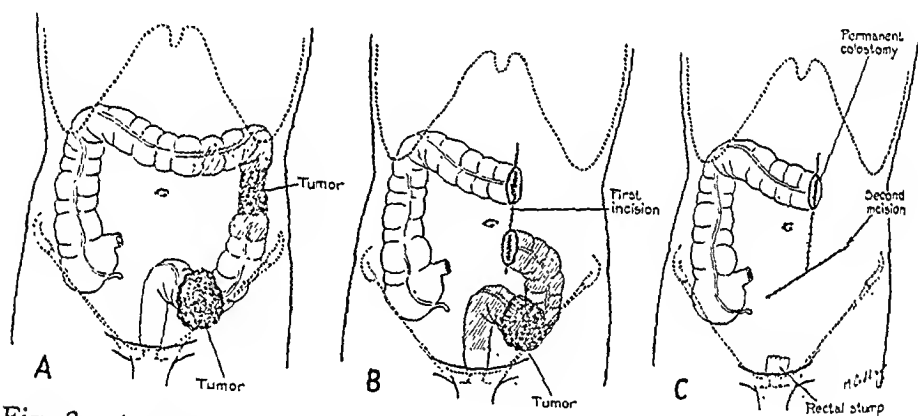


Fig. 2.—A plan used for resection of dual carcinoma of the colon when the distal growth is an extensive one of doubtful operability. A period of three weeks elapsed between the two stages.

The plan of resection is shown in figure 2. It constitutes an application of the principle of the Lahey two stage resection⁴ to a low sigmoidal growth of doubtful operability. Ordinarily it would not be used except for a lesion in the rectum, but the presence of a dual lesion, one of which was of borderline operability, made it desirable. After operation the distal colon was irrigated daily, and at the end of three weeks the second operation was performed. This was done through an oblique incision in the lower part of the abdomen; the incision included the lower end of the first incision (fig. 2). There was an amazing regression of the size of the tumor mass. It was now possible to free it from the small bowel. The apparent extension to the bladder and abdominal wall was confined to the peritoneal surfaces so that the entire lesion was easily removable. This was accomplished again by means of an anterior resection, by which the superior hemorrhoidal vessels were destroyed and all the pelvic colon was removed. The rectal stump was closed but again left intraperitoneally. Convalescence was uneventful. This

4. Lahey, F. H., and Cattell, R. B.: Two-Stage Abdominoperineal Resection of the Rectum and Rectosigmoid for Carcinoma, *Am. J. Surg.* 27:201 (Feb.) 1935

patient was alive and well at the time of writing, two years since operation. This, again, represents the adoption of anterior resection to permit of a more radical attack on an extensive lesion of the lower part of the sigmoid. I believe that the use of a two stage procedure in this manner permitted the resection of a sigmoidal growth which might otherwise have been considered, and, if attempted in one stage, might have proved inoperable.

AVOIDANCE OF COLOSTOMY

To advocate anterior resection as a means of avoiding colostomy in cases of cancer of the upper part of the rectum is dangerous. Recurrent cancer is too high a price to pay for avoiding colostomy. On the other hand, there are a considerable number of cases of cancer of the rectosigmoid or the lower part of the sigmoid in which an adequate resection must include the superior hemorrhoidal vessels but in which an abdominoperineal resection is not necessary. The comparative areas removed

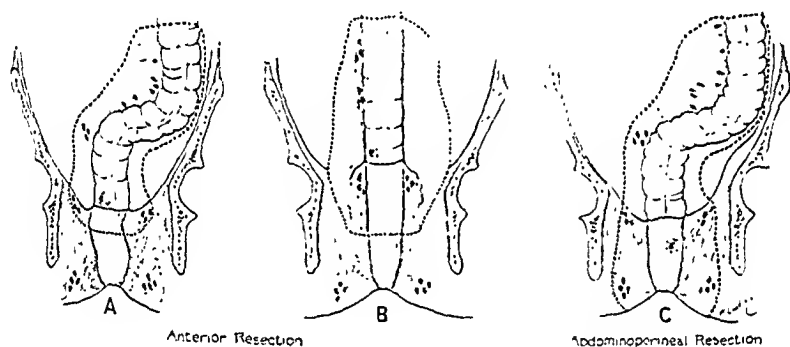


Fig. 3.—The comparative extent of the resections accomplished by the anterior (A and B) and the combined abdominoperineal resection (C). Anterior resection should be employed for a tumor of the rectosigmoid only when an adequate margin can be developed below the tumor by freeing the rectum from the hollow of the sacrum (B).

by anterior resection and abdominoperineal resection are shown in figure 3. It can be seen that if the lesion is sufficiently high, enough room is gained by freeing the rectum from the hollow of the sacrum to permit fully as extensive a resection as is accomplished when a low-lying rectal lesion is removed by the combined route. Only when there is room for adequate resection by the anterior route should the operation be utilized, and it is only under these circumstances that avoidance of permanent colostomy can justifiably be permitted. The precise indications for anterior resection as opposed to abdominoperineal resection await clarification on the basis of careful pathologic study of resected specimens and follow-up data gathered over a long period.

TECHNIC OF ANTERIOR RESECTION

There are three indications for preliminary colostomy, namely, intestinal obstruction, a large growth of borderline operability and contemplated immediate end to end anastomosis. Sometimes colostomy is done as a preliminary procedure; at other times the region of the growth is first explored and then, if necessary, colostomy is performed. When anterior resection with closure of the rectal stump is contemplated, preliminary colostomy is rarely indicated.

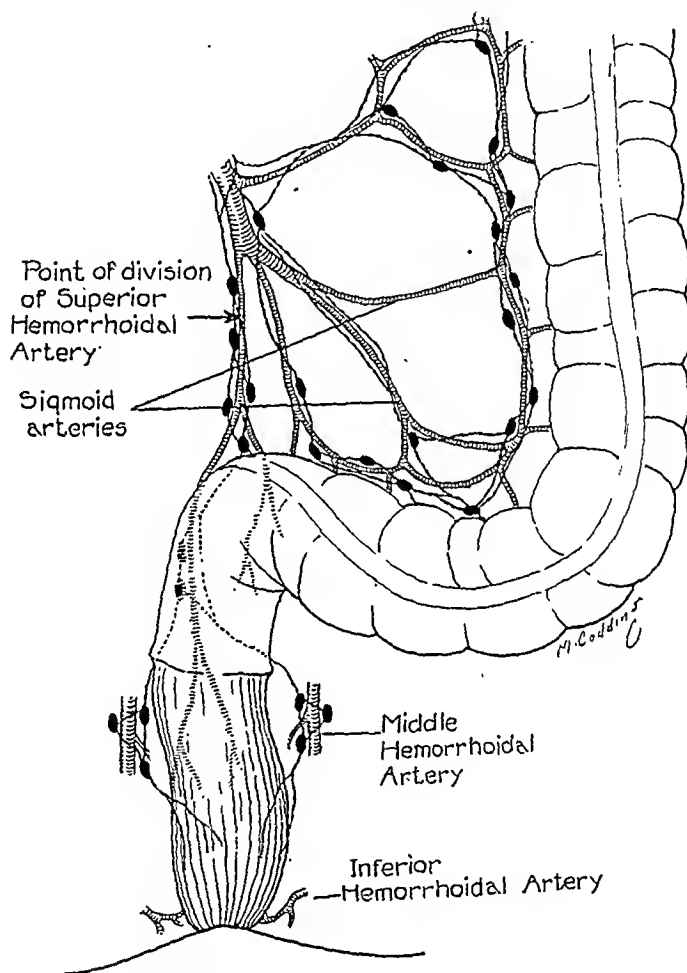


Fig. 4.—Point of ligation of the superior hemorrhoidal artery in anterior resection. If anastomosis is contemplated, great care must be taken to preserve the lower part of the sigmoid and the marginal branch of the sigmoid arteries.

Colostomy is best done on the right side of the transverse colon; this permits mobilization of the splenic flexure in the event that there is an unusually short sigmoid loop. In my experience transverse colostomy of the permanent type, as advocated by Cheever,⁵ has proved the most satisfactory means of preparing the distal colon for resection. It is

5. Cheever, D.: The Choice of Operation in Carcinoma of the Colon. *Ann Surg.* 94:705 (Oct.) 1931.

superior to cecostomy because it completely diverts the fecal stream. Compared with a Devine colostomy⁶ it is a less serious operation for the patient and is easier to make and much easier to close for the surgeon, and we believe it provides for fully as satisfactory cleansing of the distal colon.

Resection is performed ten days to three weeks after colostomy. The abdomen is opened through a left paramedian incision, the rectus muscle being laterally retracted. After determination of the extent and the operability of the growth (unless this has been done at the time of

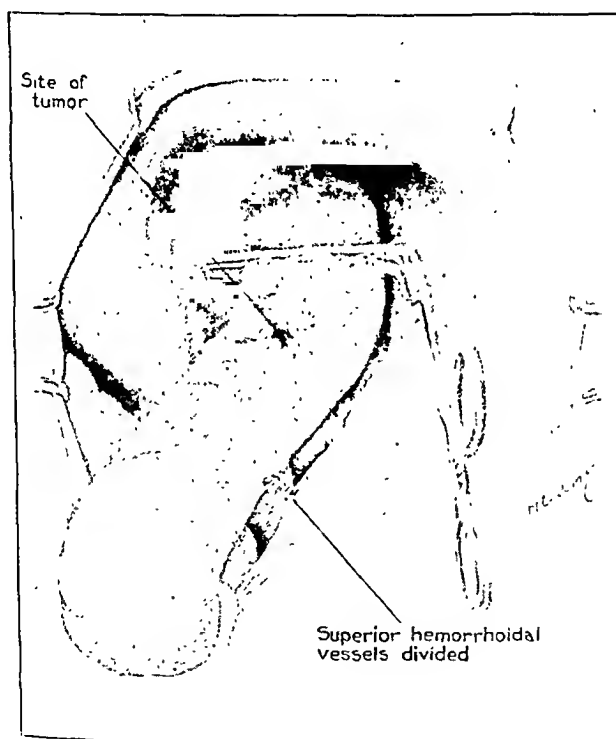


Fig. 5.—Anterior resection of the rectum. The ureters have been identified; the superior hemorrhoidal artery has been divided, and the pelvic colon freed down to the suspensory ligaments of the rectum. A right-angled clamp is placed across the bowel well below the tumor.

colostomy), the peritoneal reflections of the pelvic mesosigmoid are opened from just above the promontory to the hollow of the sacrum. The pelvic colon is mobilized and the ureters identified. The superior hemorrhoidal artery is then divided below the last sigmoidal branch (fig. 4). The peritoneum is then opened anteriorly between the bladder or the uterus and the rectum, and the entire bowel is freed, care being

6. Devine, H.: Excision of Rectum, *Brit. J. Surg.* **25**:351 (Oct.) 1937.

taken not to injure the region of the middle hemorrhoidal vessels. If by these maneuvers a generous margin has been developed below the tumor, anterior resection is done. The upper part of the sigmoid is divided between clamps, and then a right-angled clamp is placed across the lower segment (fig. 5). As the bowel is divided below this point, the rectum is secured with Allis forceps (fig. 6). There is little or no danger of spilling or leakage from the lower segment, but this maneuver assures a clean field while the bowel is being divided and yet does not compromise the blood supply of the lower segment by crushing it in a

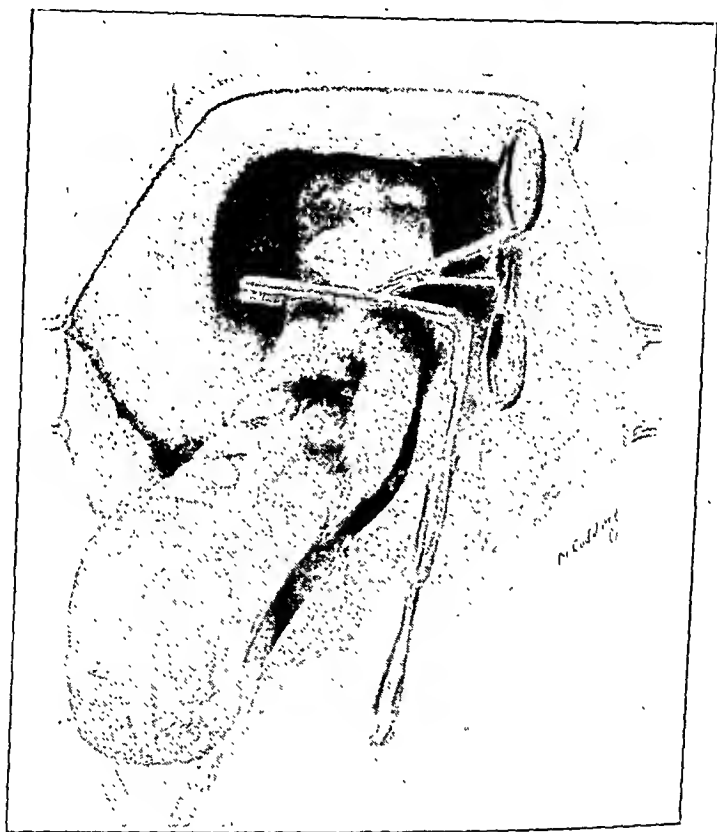


Fig. 6.—Anterior resection of the rectum. A distal clamp is not used. As the bowel is divided with the cautery, the stump of the rectum is secured with Allis forceps.

clamp. After removal of the tumor the lower segment is closed by a continuous inverting suture of fine catgut on an atraumatic needle, reinforced with serosal sutures of fine silk. If anastomosis is planned, the procedure is as follows: By gentle traction on the Allis forceps the lower segment is elevated while the upper segment is brought down to it, and the posterior layer of serosal sutures is placed and tied (fig. 7 A). The Allis forceps are then removed; the bowel is opened, and the anastomosis is completed (fig. 7 B, C). A curved spring-bladed enterostomy clamp is kept on the upper segment during anastomosis (fig. 7). I

believe that an open anastomosis is preferable to a closed anastomosis in this situation because it permits one to be certain of an adequate blood supply to the resected ends of the bowel and because it assures accurate placing of sutures, assuring a water-tight anastomosis.⁷ After completion of the anastomosis the peritoneal floor is closed. In the 2 cases included in this study the anastomosis was left below the reconstructed pelvic floor. It is advisable to drain the retroperitoneal space whenever the line of resection is left below the peritoneal floor. The colostomy is closed ten days to three weeks after the resection. This is a comparatively minor procedure, readily done with the area under local anesthesia.

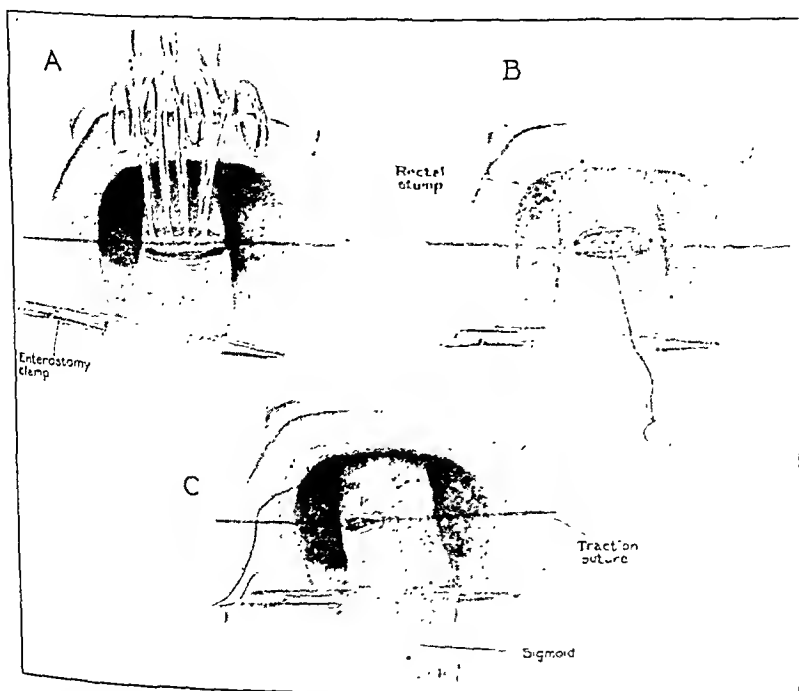


Fig. 7.—Anterior resection of the rectum. After division of the bowel, the distal stump is closed with a continuous inverting suture of catgut, reenforced with serosal sutures of silk; or, in exceptional cases, anastomosis is performed as shown.

SUMMARY

Recent experiences with anterior resection in the management of cancer of the rectosigmoid are recorded. Emphasis is placed on the use of this procedure to extend the scope of resection in cases of lesions of the lower part of the sigmoid rather than to limit the areas of resection in cases of cancer of the upper part of the rectum. A technic of resection which has proved satisfactory is outlined.

7. Cutler, E. C., and Zollinger, R.: *Atlas of Surgical Operations*, New York, The Macmillan Company, 1939.

SURGICAL ASPECTS OF PAIN IN THE ABDOMEN IN RELATION TO CLAIMS FOR COMPENSATION

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If the physician is to evaluate the symptom of abdominal pain as a basis for compensation, he should be alert in determining its significance by obtaining a detailed history and carrying out a careful examination supplemented by appropriate laboratory study. For pain is a universal symptom, and if it is preponderant, there may be difficulty in establishing its significance with respect to a claim for compensation. The pain must be proved to be the result of a compensable cause.

In relation to compensation, pain in the abdomen may be divided into three categories:

First there is pain in the abdomen resulting from the specific hazards of an occupation, as for instance painter's colic or the pain associated with hematuria resulting from the specific tumor of the bladder which occurs in aniline dye workers. The history and the physical examination will establish pain of this type as clearly the result of an occupational hazard and, as such, it reasonably entitles the patient to compensation.

The second type of pain in the abdomen is that produced by trauma in a patient otherwise free from disease. Such trauma includes not only injury by a sharp or a blunt object but likewise that resulting from muscular contraction, as in the strain of lifting, or from a fall. The first evidence of abdominal trauma is pain, but its intensity, distribution and persistence will vary according to the effect of the trauma on the walls or on the viscera and other structures of the abdomen.

In the third category is pain which is the effect of occupation and especially of occupational trauma on a preexisting lesion in the abdomen. This group demands careful determination of the many factors involved. What would have been the natural course of the disease, for example, is an important question in evaluating the effect of a fall in precipitating gastric hemorrhage in a patient with peptic ulcer.

Presented at the meeting of the Association for the Advancement of Industrial Medicine and Surgery, May 1941.

From the departments of surgery of the Flower and Fifth Avenue Hospitals and the Metropolitan Hospital.

The need of establishing exactly the relation of trauma to an abdominal lesion is emphasized by the following case in which much confusion resulted from a clear history of previous injury.

CASE 1.—H. P., a 28 year old elevator operator, was admitted on Aug. 10, 1937 and discharged on September 25. His chief complaint was pain in the upper left quadrant of the abdomen and in the left shoulder. The pain began three weeks before admission; it became severe the last few days and fever developed before admission. He had lost 15 pounds (6.8 Kg.) in the last month. He stated that ten years prior to this he had been struck by a plank across the epigastrium but that there had been few symptoms and he had recovered in a few days. One week before admission, he felt that he had injured himself diving in a pool. He laid great stress on both these injuries and repeatedly called attention to them.

His temperature on admission was 100.6 F., and he had a continuous low fever until the time of operation; the pulse rate was normal. Examination revealed a mass in the upper left quadrant of the abdomen; this was tender and conformed in every particular to an enlarged spleen. Because of this observation, detailed studies of the blood were made, but they revealed no abnormalities. Slight rigidity and distention and definite tenderness were present in the abdomen. The chest was normal. Roentgen studies included a complete series of gastrointestinal roentgenograms, an intravenous urogram and a pneumoperitoneal study. The mass demonstrated by these studies was interpreted as an enlarged spleen displacing the stomach toward the midline and the splenic flexure downward. There was no other abnormality in the stomach or the intestine; however, the left kidney was not visualized. As my associates and I observed the mass on various occasions, several of us felt that it was increasing in size. The left kidney could be palpated below and behind the mass, which in addition to becoming progressively slightly larger, became also more tender.

The impression was given that there was a slow hemorrhage from a trauma of the spleen, which was possibly well encapsulated, an enlarged spleen with a twisted pedicle (traumatic) or perisplenitis (traumatic). It was decided to operate. Through a left rectus incision an enormous retroperitoneal tumor was demonstrated; this had simply compressed and fixed the spleen against the ribs. On mobilization this tumor was readily delivered just over the kidney to which it was affixed. The kidney itself was grossly normal, except for a few cysts. The adrenal gland was incorporated in the capsule of the tumor, the main blood supply of which was derived from the renal vessels. The tumor and the kidney were removed intact. The tumor after fixation measured 19 by 16 by 14 cm. in diameter. On histologic examination it proved to be a myxosarcoma. The kidney was atrophied and the adrenal gland showed cortical hyperplasia, but neither revealed any evidence of neoplasm. After operation he was given roentgen therapy and at the time of writing has remained well, except for one minor attack of flatus attributed to an orgy of "hot dogs" and beer.

The emphasis on the trauma in this history led to the assumption that some trauma of the spleen due to the injury by the plank had been activated by the dive in the pool and had produced slow hemorrhage. While the dive may have been a factor in directing attention to the abdomen, it is probable, since there was no evidence of hemorrhage in the vicinity of the tumor, that the dive was in no way responsible for this

man having a retroperitoneal tumor. I leave it to the reader to decide whether trauma from a plank striking across the abdomen ten years before could cause a myxosarcoma originating in the retroperitoneal tissues.

The preponderance of pain in the later manifestations after abdominal trauma is important not only as a consideration in determining what surgical care the patient should receive but also as a potential basis of claims for indemnity. Since the legal status of pain is primarily determined by medical testimony, the physician should be alert to the importance of a proper evaluation of the role of trauma in arriving at a diagnosis.

A case may serve to illustrate one extreme of the wide variation in the relation of trauma to persistent pain in the abdomen.

CASE 2.—M. V., a 25 year old porter, was admitted for emergency treatment. He complained of severe pain in the abdomen with diffuse distention and tenderness. He stated that eight days before an iron bar had struck him on the head and the abdomen; he was vague as to what had happened since. The first diagnostic impression was "possible retroperitoneal hematoma." He was carefully observed for ten days, but complete physical, laboratory and roentgen examinations failed to bring to light any abnormalities. However, there was increasing evidence of what was finally diagnosed as a fear reaction. My associates and I were finally able to gain his confidence and convince him that he had escaped any of the serious ruptures he supposed should follow the injury. He was discharged but maintained under the care of a neuropsychiatrist and followed for several months, long enough to confirm that the whole trouble was essentially a fear pain. Certainly there never was evidence of any organic lesion, except flatus, that universal handmaid of the neurotic abdomen.

It must be remembered that severe strains of the muscles and blows on the abdomen may produce effects which depend on the fact that the abdominal cavity contains gas-filled organs, as well as solid viscera, with large blood vessels. The compressing action will vary according to whether the blow or the strain encounters a solid organ against a bony framework, such as the liver under the rib margin, or is exerted against the gas-filled compressible viscera.

Trauma from direct blows may involve any portion of the wall of the abdomen; it results in a varying degree of contusion with associated ecchymosis. This may involve the front of the abdomen but is more common over the lateral walls and the region of the loins. It is a well known fact that severe blows limited to a small area are more likely to result in extensive injury of the intestine and the mesentery than widespread trauma, which may result in lacerations of the liver, the spleen or the kidney. After a fall or a blow produced by a broad surface or a contusing force, such contusions may or may not be associated with contusions or ruptures of the viscera. As a rule, however, the patient experiences sharp pain with a moderate degree of shock; he recovers

from this with subsequent soreness of the wall of the abdomen followed by discoloration which varies in extent and is usually more marked along the iliac crest, where the blood tends to gravitate. Tenderness without marked rigidity and the absence of continued shock and hemorrhage are different from the initial symptoms of visceral injuries. There may be no evidence whatever of contusion of the wall of the abdomen in cases of severe injuries of the viscera, but shock and evidence of hemorrhage and peritonitis follow in fairly rapid order.

While in my experience there have been several instances of extensive hemorrhage after contusing injuries of the extremities, there has not been a single example of a severe hemorrhage in the muscles of the wall of the abdomen after contusion. On the other hand, there have been 2 instances of extensive hemorrhage in the right rectus muscle without any history of trauma.

CASE 3.—A. M., a 42 year old white woman, was admitted April 30, 1941 with the chief complaint of sharp pain in the right lower quadrant of the abdomen. She had been perfectly well until eight hours before admission. At that time (6 a. m.) she rolled over in bed and felt a sudden sharp stabbing pain in the right lower quadrant of the abdomen. This pain persisted constant and sharp. The last bowel movement on the previous day had been normal. The menstrual periods usually occurred every twenty-five to twenty-eight days and lasted for seven days. At the last period, one week before admission, the flow had been profuse with large clots; there had been no cramps; the previous period had been skipped, but the others had been regular. The patient had been examined one year before in a gynecologic clinic; at that time the uterus was slightly enlarged and anterior; there were no adnexal masses.

She was obese and slightly pale and was in acute pain. Her heart was enlarged 14 cm. to the left. Her pulse rate was $\times 80$; her blood pressure was 154 systolic and 85 diastolic. There was a harsh systolic apical murmur. Palpation of the abdomen revealed a grapefruit-sized mass in the right lower quadrant, midway between the anterosuperior spine and the umbilicus. The mass was firm, extremely tender and easily felt, and the abdomen seemed to be freely movable over it. Examination of the pelvis and the rectum revealed a normal uterus and adnexa; the mass could not be palpated. The blood and the urine were normal.

The preoperative diagnosis was ovarian cyst with twisted pedicle, a degenerating pedunculated fibroid.

Dilation and curettage were performed. The rectus sheath was exposed through a lower midline incision and was found to be purple. The sheath was opened, and the entire right lower rectus muscle was observed to be necrotic and surrounded by about 6 ounces (177 cc.) of clotted blood. The right inferior deep epigastric artery was found to be actively spurting; it was clamped and tied. The peritoneal cavity was not opened. Closure of the incision was accomplished with plain 0 and chronic no. 1 catgut with a superficial drain. The patient was discharged in twelve days.

In this case, therefore, an extensive hematoma of the right rectus muscle simulating a pelvic tumor occurred without trauma and resulted from hemorrhage from the superficial epigastric artery without known cause.

The relation of trauma to lesions of the gastrointestinal tract has been carefully reviewed in the literature. Gerendasy and Crohn,¹ Eusterman and Mayo,² Gray³ and others have reported ulcers of the stomach and the duodenum which followed direct abdominal trauma and were alleged to have resulted solely from such trauma. In a study of 121 cases of pancreatic cyst, Korte found a definite history of trauma in 27 per cent, such cysts being really peripancreatic with a collection of fluid caused by necrosis of the fat in the lesser omental sac.

Lévai investigated a series of 1,054 cases of appendicitis; in 9 there was a history of trauma from strain of lifting or from falls or blows. However, he expressed the opinion that the trauma activated rather than initiated the acute attack in a previously diseased appendix. There have been published reports of a few cases in which there were definite traumatic lesions, usually tears of the mesoappendix; these lesions correspond to the severe traumatisms found in the small intestine.

Aside from rupture, the evidence of severe trauma at operation includes a tear in the mesentery, areas of ecchymosis of the serosa or submucous hemorrhage. It is conceivable that in cases of so-called obstructive appendicitis trauma may distend the lumen of the appendix by forcing fecal material under pressure, thus simulating an attack in a previously diseased appendix. But since in the overwhelming majority of cases in which such a mechanism is present appendicitis occurs spontaneously without any trauma, it would be necessary to establish clearly that without previous symptoms signs of appendicitis followed directly and consecutively after the trauma.

In a total of 1,452 admissions I have been unable to find a single instance of a definite relation of trauma to the abdominal lesions of appendicitis, cholecystitis or gastric or duodenal ulcer. There were 9 cases in this series in which there were definite traumatic lesions of the abdomen; in 2 there was rupture of the bladder and in 2 there was severe contusion of the kidney; in 2 cases the diagnosis was retroperitoneal hemorrhage. In all of these cases the patients recovered. There was 1 case of rupture of the spleen and the jejunum, the history of which is as follows:

CASE 4.—R. C., a 7 year old boy, was struck across the abdomen by a stone balustrade when the platform on which he was standing collapsed. He was immediately brought to the hospital and admitted in severe shock; he was pale, and

1. Crohn, B. B., and Gerendasy, J.: Traumatic Ulcer of Duodenum and Stomach, *J. A. M. A.* **100**:1653 (May 27) 1933. Gerendasy, J.: Traumatic Peptic Ulcer, *Am. J. Surg.* **21**:12 (July) 1933.

2. Eusterman, G. B., and Mayo, J. G.: Traumatic Peptic Ulcer, *Am. J. Surg.* **26**:74 (Oct.) 1934.

3. Gray, I.: External Trauma in Relation to Ulcer of Stomach and Duodenum: Report of Five Cases, *Ann. Int. Med.* **7**:1403 (May) 1934.

his pulse rate was 150. His blood pressure was 90 systolic and 50 diastolic. The abdomen was becoming rapidly distended, rigid and markedly tender. There was no ecchymosis except a slight trauma of one foot. The blood counts were: hemoglobin, 70 per cent; red blood cells, 4,000,000; white blood cells, 38,300; polymorphonuclears, 81 per cent. Two hours later the blood counts were: hemoglobin, 63 per cent; red blood cells, 3,000,000; white blood cells, 29,000; polymorphonuclears, 91 per cent.

Operation revealed a laceration of the jejunum, which was torn across 2 inches (5 cm.) from Treitz's muscle, an extensive cracked eggshell laceration of the spleen and a tearing away of the splenic flexure. Rapid splenectomy and side to side intestinal anastomosis were done. The patient died a few hours later.

In reviewing a series of 57 cases of perforation of gastric ulcer I found no evidence of trauma in any instance. Perforation of the peptic ulcer did not seem to be precipitated by any factor related to the occupational activities of the patient. Perforations sometimes occurred after physical effort at work, but in the majority of cases they occurred while the patient was not actively engaged in any exertion, many occurring in the night. While in 1 or 2 instances in a large series of cases of appendicitis in the combined services at the Flower and Fifth Avenue Hospitals and the Metropolitan Hospital some traumatic factor has figured in the history, there has not been encountered a single example of appendicitis in which there was any evidence that trauma was primarily responsible.

A better understanding of the mechanism of abdominal pain and its distribution will be had by considering the structural components of the abdomen. These consist of a cavity surrounded by voluntary muscles supplied by the spinal nerves derived from the lower six thoracic and the first lumbar nerve and of the diaphragm supplied on its inferior surface by the phrenic nerve derived from the fourth cervical segment. The cavity contains viscera supplied largely by the splanchnic nerves with sympathetic parasympathetic fibers determining spasm or dilation of the lumens of the hollow viscera. Pain may result from inflammatory or traumatic irritation and is invariably associated with tenderness and rigidity. Further, pain may result from direct or distant irritation of the neural pathways. As a consequence, severe abdominal pain simulating a lesion may be caused by an extra-abdominal pathologic condition, just as the pain referred to the abdomen in cases of pneumonia in children simulates appendicitis and epigastric pain simulates peptic ulcer or cholecystitis in cases of angina; there is also the severe pain with hyperesthesia of the abdominal wall seen in cases of shingles or of lesions of the spine itself. The importance of careful control by obtaining a detailed history and making a careful physical examination of the symptom of pain is evident. Another factor to be considered is the variability of the threshold of pain according to the age and the sensitivity of the patient. These factors must be appraised in evaluating any claim

on the part of the patient that disability pain is the result of an occupational hazard, especially if few physical findings are evident. It has been said that the abdomen is the sounding board of the emotions. If the pain is the result of a traumatic lesion to which it is alleged to be related, this fact is usually susceptible of proof. In cases of abdominal pain, whether direct or referred, which is the result of an organic anomaly not itself the result of an occupational hazard nor attributable to trauma, claims for compensation can be established only by proving that the lesion would not in itself have caused the pain and associated symptoms without the particular exciting factor.

In cases of hernia, the factor of trauma is paramount in establishing a claim for compensation based on a history of the sudden onset of pain with or without a perineal bulge after strain or trauma sustained while working. This applies not only to the inguinal variety but to the other forms as well. Even in cases of incisional hernia (usually associated with intestinal or omental adhesions) such a history results in a claim for compensation. Such a case is that of a bartender who had had an incisional ventral hernia for twenty years after an appendectomy. After lifting a heavy case, he experienced severe pain, and the protrusion greatly increased in size. He was operated on a few hours later. In the omentum, which was adherent in the hernial sac, there was evidence of recent hemorrhage and of a new torsion of a segment of the omentum, probably the result of the trauma caused by the strain.

There is often a distinct and definite history of the appearance of a hernial bulge, of pain after a strain or of some trauma sustained while the patient was at work. In cases of postoperative intestinal adhesions the history often reveals the most typical symptom, pain induced by physical effort, straining or other factors involving trauma. In such cases, abdominal pain may be considered to have an important relation to claims for compensation. There can be no question of the definite relation of severe physical strain to hernia, and in these cases such strain may produce an increased protrusion or even incarceration. The degree of disability produced seems to justify a claim for compensation, even though surgeons recognize that the factor primarily responsible for the hernia is an anatomic defect. In cases of postoperative incisional hernia, in which adhesions play so important a part, abdominal strain resulting from certain occupational hazards or from injuries may produce a serious intra-abdominal lesion. The important point is that the lesion had not occurred before the trauma.

What is the emotional nervous background of the person seeking compensation and presenting pain as the prominent symptom? The answer to this question must be well considered. The burden of proof devolves on the doctor who denies the persistence of pain on the grounds of neurosis. In such cases disability entitling to compensation can be

denied only after a complete study has excluded all other possible explanations. In the search for a cause of pain in the abdomen sufficient to substantiate a claim for disability, roentgen examination offers visible evidence in contrast with the intangible evidence afforded by the history. It is in this group of cases that controversy most often arises. Tangible proof may settle what otherwise would continue as a merely academic discussion of the causation of the pain.

Pain, then, may result from many different factors; these should be evaluated in estimating whether the particular complaint is compensable. It should be borne in mind that if the pain is the result of the traumatic lesion to which it is alleged to be related, this fact is usually susceptible of proof. In cases of pain in the abdomen, whether direct or referred, the result of an organic lesion not itself the result of an occupational hazard or attributable to trauma, claims for compensation can be established only by proof that the lesion would not of itself have caused the pain and associated symptoms without the particular exciting factor.

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REVIEW OF UROLOGIC SURGERY

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KIDNEY

Surgical Procedures.—Rolnick and Singer¹ discuss contralateral massive collapse of the lung after operation on the kidney. This condition is rarely fatal and therefore often overlooked, particularly when minor degrees of involvement are present. If atelectasis persists for several days, it may be followed by infection of a mild pneumonic type, and then true postoperative pneumonia may be simulated.

This condition is often diagnosed as postoperative pneumonia because of the cyanosis, dyspnea and considerable increase of temperature above normal that almost invariably accompany atelectasis.

Atelectasis may follow any operative procedure, but it occurs most frequently after operation on the upper part of the abdomen. The direct etiologic factor is the accumulation of mucus and the retention of it within the bronchi followed by the formation of a mucous plug which blocks one or more bronchi.

Atelectasis may follow any type of anesthesia—inhalation, local or spinal. It also occurs when there is no increase of bronchial secretion

1. Rolnick, H. C., and Singer, P. L.: Contralateral Massive Collapse of the Lung in Kidney Surgery, *J. Urol.* 45:678-681 (May) 1941.

Preliminary administration of atropine may be a factor in producing the condition, since atropine does not diminish the secretion of mucus but merely concentrates it, thus helping to form a plug.

During and immediately after the operation, material in the larynx, the pharynx and the bronchi should be well aspirated. If this is done, the incidence of atelectasis will be markedly reduced.

. Only a few instances of atelectasis after operation on the kidneys and on the upper portions of the ureters have been reported. In all, the condition occurred on the side opposite to that operated on; that is, the side on which the patient had been lying on an elevated kidney rest. With the patient in this rather difficult position, marked compression of that side of the thorax occurs during the entire operation, so that this is a site favorable to the development of atelectasis.

During the past ten to twelve years Rolnick and Singer observed 6 instances of atelectasis following operation on the kidneys and on the upper part of the ureters.

The enforcement of postural drainage is an essential factor in the rapid recovery of patients, along with the administration of expectorants and drugs which have an action opposite to that of atropine. Should the patient be gravely ill and should the long-continued spontaneous resolution of the atelectasis be too great a burden for the patient to bear, bronchoscopic removal of the plug of mucus is indicated. This is the most rapid and satisfactory method of relief of postoperative atelectasis. Bronchoscopic removal of mucous plugs is a routine procedure in some institutions.

Muschat² advises the use of balloon catheters for drainage after nephrostomy.

No adhesive plaster is required, because the filled balloon cannot come out. Introduction or replacement is painless and easy for the patient and the surgeon alike. Latex catheters are pliable and do not kink easily. They do not become lined with urinary salts as readily as the older kind. Removal and replacement are not complicated and can easily be accomplished by an attending nurse or even by a member of the patient's family. Filling the balloon is simple, and water or mineral oil can be used. Air should not be used, for it escapes within a few days, regardless of how tightly the inflation tube is secured. The wound remains clean, and after removal of the first granulation tissue, it continues to appear wholesome with little discharge.

If the patient is a man, a metal flask is placed in the regular hip pocket of the trousers, and the tube is placed within it after an opening has been cut through the shirt. This arrangement, and this one only,

2. Muschat, M.: Nephrostomy Drainage: The Use of Balloon Catheters, *J. Urol.* 45:652-653 (May) 1941.

permits free motion, allows the patient to get up and sit down without discomfort and, what is more important, allows him to do these things without spilling.

McKenna and Kiefer³ state that conservative operations have been done for some time in cases in which nephrectomy was impossible, such as, usually, those in which the opposite kidney was absent or functionless. The good results obtained in some of these cases have encouraged urologists to use these conservative procedures in more and more cases in which more radical procedures are not required.

A kidney the function of which has been held in abeyance by obstruction may be found at operation to have a large amount of apparently good renal tissue. The status of each kidney in the matter of infection should be studied completely in every case. Pyelography should be utilized to the fullest to get the most nearly accurate picture possible of the anatomic conditions present. When all the pertinent data have been accumulated, the surgeon must try to reach a decision as to the type of operation best suited to the condition at hand.

When the decision to do a conservative surgical procedure finally has been reached, the preoperative preparation must next be considered. The presence or absence of infection is a major consideration. Whereas nephrectomy, even with a badly infected kidney, usually can be done without gross contamination of the operative field, in many conservative operations the urinary tract must be opened, and any infective process present is spread to the large open surfaces of the wound.

At the time of operation, considerably more care must be exercised than is necessary with nephrectomy. Adequate exposure is more difficult to obtain but is even more essential than when the kidney is being removed. Meticulous attention to detail is necessary. Where the renal parenchyma is cut, hemostasis must be complete and effected in such a way as not to cause destruction of additional tissue. Nephrostomy and pyelotomy tubes must be accurately and carefully placed.

The patients on whom some conservative procedure has been done require more postoperative care and attention than patients who have had the kidney removed. This is true chiefly when some form of urinary diversion has been used. The drainage tubes require almost continuous watching by trained personnel.

Nephrostomy is, in McKenna and Kiefer's opinion, the most valuable of the conservative renal operations. At first used only as a means of permanent urinary diversion, it has been almost universally replaced in that role by ureterosigmoidostomy and cutaneous ureterostomy. At present it is used almost entirely for temporary short-circuiting of the urinary stream.

3. McKenna, C. M., and Kiefer, J. H.: *Conservative Renal Surgery*, J. Urol. 45:272-281 (March) 1941.

Seriously sick patients, whose ability to tolerate nephrectomy is doubtful, can undergo nephrostomy under local anesthesia if necessary. The freedom from toxic absorption, the improved urinary drainage and the direct access to the renal pelvis for lavage usually lead to a great improvement in the patient's general condition and often to a striking improvement in the local condition of the kidney as well.

In cases of obstructive anuria nephrostomy may be a life-saving measure, and in cases of this type in which the risk is bad the operation should precede attempts at direct removal of the obstruction.

For anuria of the nonobstructive type, McKenna and Kiefer have employed nephrostomy and decapsulation with success in about half the cases.

Wilhelm,⁴ in discussing the McKenna and Kiefer article on conservative renal surgical procedures, states that in no field is conservatism more important than in the treatment of hydronephrosis caused by non-calculous obstruction at the ureteropelvic junction. He collected and analyzed the results of the 32 plastic operations on the renal pelvis and ureters which had been done at the Mount Sinai and Beth Israel hospitals in the twelve years prior to the time of his discussion. In cases of bilateral renal disease with uremia or with impending uremia, he makes it a practice, he says, to operate first on that kidney which apparently has the better function. If this kidney has been saved by performance of nephrostomy or, possibly, by a conservative plastic operation, the remaining side can be operated on with increased safety.

Anomalies.—Pierson and Honke⁵ report a case of unilateral fused kidney with bilateral ureteral bifurcation afflicting a woman 58 years old who had persistent pyuria. She had been told on several occasions that the urine contained pus. Cystoscopic examination showed chronic cystitis to be present. Both ureteral orifices were in the normal positions. Catheters were passed without meeting obstruction in either ureter. A plain roentgenogram showed the left catheter to pass somewhat laterally to its normal course and the right catheter to cross the midline over the upper portion of the sacrum. Retrograde pyelograms demonstrated bifurcation of the left ureter at the junction of the upper two thirds and the lower third, with incomplete rotation of the entire left kidney so that the ureteral branch to the upper segment ran laterally to the lower and larger renal pelvis. The right kidney lay over the fourth and fifth lumbar vertebrae in the midline with a bifurcated ureter crossing from the right side.

4. Wilhelm, S. F., in discussion on papers of Lowsley and Menning²⁴ and McKenna and Kiefer,³ J. Urol. 45:282-289 (March) 1941.

5. Pierson, L. E., and Honke, E. M.: Unilateral Fused Kidney with Bilateral Ureteral Bifurcation, J. Urol. 45:682-684 (May) 1941.

Various urinary complications have been discovered in association with unilateral fusion anomalies. These vary from simple infection to additional types of congenital anomalies. Five reports in the literature definitely describe bifurcation of the ureter in association with unilateral fusion.

From this series, consisting of the case reported by Pierson and Honke in addition to 5 cases collected from the literature, a few observations may be obtained. Three of the patients died within the first ten months of life. Except for 1 patient whose sex was not stated, these 3 patients who died within the first ten months were males and included all the males in the series. The 3 female patients of the series lived to adult age. In 4 cases the fused mass lay on the right side, compared with 2 cases in which it lay on the left side.

In only 2 of the patients was the condition diagnosed before death. Pierson and Honke stated that in 1913 Rathbun found a left ureter bifurcated over the sacral promontory with right-sided fusion of both kidneys.

Ercole⁶ reports 2 cases of horseshoe kidney in which he operated. Associated lithiasis was present in both. The approach in each case was made through an anatomic lumbar incision, a method which permits sufficient exteriorization of the isthmus.

In the first case, the fact that the two lower poles were in such close relationship that an isthmus hardly existed (the two being bound solidly together by a dense mass of parenchyma) and the additional fact that a lower polar vessel entered the kidney at the level of the isthmus led Ercole to give up the idea of performing symphysiotomy and to do instead simple pyelotomy for extraction of the calculus. This was the more logical procedure in view of the fact that the patient suffered only from the presence of the stone and not from any symptoms referable to the horseshoe malformation itself.

In the second case the isthmus, which likewise was composed of renal parenchyma, could be sectioned easily, and the stone could be extracted through an anterior pyelotomy opening. In this instance the preliminary placing of a clamp, with a view to severance of the isthmus in layers (which might be practicable if the isthmus were fibrous), would have constituted a definite disadvantage, since renal parenchyma is friable and may be easily torn by a clamp. Ercole also found that the placing of detached sutures for hemostasis, as Papin advised, is difficult, since, if the capsule is not resistant, it tears when the knot is tied. Ligature en bloc seems the simplest procedure and was carried out without complication in 4 cases in which Ercole used it.

6. Ercole, R.: Riñon en herradura y cirugía conservadora a propósito de nuevas observaciones personales, *Rev. argent. de urol.* 9:343-351 (July-Aug.) 1941.

Foley⁷ reports 6 cases of horseshoe kidney in which he has carried out symphysiotomy followed by nephropexy during the last ten years. In all but 1 of these cases (complicated by an incompletely removed stone) results have been completely satisfactory, after a period of from three to ten years. In a seventh case he did symphysiotomy for a unilateral fused kidney, also with good results. Of the 7 patients, 6 were women.

In all cases relief of pain was the chief objective. In 3 cases in which unilateral pain was present, division of the isthmus and relief of such pain were followed after a varied period by development of identical pain on the opposite side; complete relief was then provided by correction of the abnormal position of that side. In another case, originally mild pain on the opposite side gradually increased and was relieved one and a half years after the first operation by nephropexy on the second side. In 1 case of bilateral pain, division of the isthmus and nephropexy performed on only one side gave relief of pain on both sides. In the case of unilateral fused kidney, left-sided pain was relieved by symphysiotomy and nephropexy on the right. In nearly all the cases the character of the pain was fairly typical of that of pain of renal origin.

In all these cases it was possible to demonstrate obstruction and varying degrees of pelvic dilatation. In some infection of the upper part of the urinary tract and pyuria were present. In 2 cases there was unmistakable hydronephrosis, and in 1 of these the condition was complicated by stone. In none of the cases were there present merely the vague abdominal pain, constipation and other digestive disturbances that constitute the typical symptoms of horseshoe kidney disease without specific renal symptoms or renal pathologic change.

In cases in which the horseshoe kidney is observed accidentally (as, for instance, 1 in which the patient, without experiencing any kind of symptom, discovers the presence of an abdominal mass, representing the isthmus) there is no more reason to operate than there would be if an undiseased and symptomless kidney of normal form were present. In a second group Foley includes cases of horseshoe kidney in which definite frank pathologic change and symptoms of renal origin are present. In such cases it may be difficult to say what part in the symptom complex is played by the lesion and what part is played by the anomaly. Unless there are indications to the contrary, it may be best to proceed on the assumption that the associated lesion alone is responsible, to correct it surgically and to leave the anomalous relations undisturbed.

In a third group Foley places cases of horseshoe kidney in which symptoms of renal origin but not renal pathologic changes other than some degree of pelvic dilatation are present. The cases which he reports

7. Foley, F. E. B.: Surgical Correction of Horseshoe Kidney, J. A. M. A. 115:1945-1951 (Dec. 7) 1940.

belong to this group. The various degrees of pelvic dilatation in such cases are caused directly by mechanical obstruction of the ureters occasioned by the anomaly, namely, the abnormal insertion of the ureter into the pelvis and contact of the ureter with the isthmus. On the basis of his experience in the clinical management of these patients, Foley concludes that the anomalous horseshoe kidney not affected by concomitant pathologic significant change may yet be productive of pain and other symptoms and of the insidious development of renal disease and that the kidney can be restored to normal anatomic relations with relief of symptoms and arrest of the insidiously developing renal disease by division of the isthmus and nephropexy on one or both sides.

Tumor.—Bugbee⁸ states that the treatment of all renal tumor is nephrectomy if possible.

While the pathologic aspects of renal tumor are important in prognosis, a diagnosis of tumor is sufficient to warrant exploration of the kidney, unless metastasis is demonstrated, and even in the presence of metastasis an individual decision should be made in each case. In a case of the latter type operation and roentgen therapy for the metastasis represent the only chances for the patient and often are justifiable procedures. Large inoperable renal tumor can often be rendered operable by a preliminary course of roentgen therapy.

If the urologist waits for the appearance of a clearcut picture in which the diagnosis of renal tumor is certain, nephrectomy may prove to be only a palliative measure.

Painless hematuria probably is the most important early symptom of renal tumor. When suspicious deformities of the renal pelvis or calices are present in urograms, repeated examinations should be made, and if the results of such examinations are confirmed, exploratory operation on the kidney should be carried out.

The observation at operation of a kidney normal in size and contour should not dissuade the surgeon from removal of the organ if he has the courage of his convictions, based on his preoperative study of the case.

Braasch,⁹ in discussing Bugbee's paper on exploratory operation for certain types of renal tumor, states that he has observed many patients for whom a diagnosis of renal tumor had been made previous to his examination on the basis of evidence obtained in the excretory urogram. An apparent deformity suggestive of tumor often is seen in the excretory urogram which more complete visualization in the retrograde pyelogram

8. Bugbee, H. G.: Exploratory Operation for Certain Renal Tumors. *Tr. Am. A. Genito-Urin. Surgeons* **33**:25-41, 1940.

9. Braasch, W. F., in discussion on papers of Dean and McCarthy,¹⁰ Herman and Strumia,²⁰ Bugbee⁸ and Wishard,⁷⁴ *Tr. Am. A. Genito-Urin. Surgeons* **33**: 57-60, 1940.

shows is not caused by tumor. Again, the excretory urogram, because of incomplete visualization, may not disclose any deformity, and the retrograde pyelogram will visualize it. A retrograde pyelogram should be made in every case in which the condition is doubtful. Careful scrutiny of minor details in the outline of the calices should be made routinely, and in case of doubt the condition of the patient should be checked subsequently by means of frequently made retrograde pyelograms. If these precautions are taken, renal tumor can be recognized in most cases, although occasionally an exploratory operation is necessary.

Dean and McCarthy¹⁰ report a case of hemangioma of the kidney associated with diffuse hemangioma of the lower extremity. They make the report not only because of the rarity of each disease but also to emphasize the likelihood of such congenital vascular tumor affecting more than one part of the body of the same patient. In a study of 1,046 patients with tumor of the blood vessels it was noted that in a group of 9 patients suffering from diffuse hemangioma of an extremity, 2 had hemangioma of the viscera.

There is evidence in the literature that hemangioma of unusual situation or extent is often only part of a larger congenital pathologic complex. Angioma of the retina (von Hippel's disease) often accompanies angioma of the cerebellum, thus constituting still another disease complex known as Lindau's disease. Angioma of the central nervous system is frequently associated with cyst of the pancreas or kidney, whereas the common multiple hemangioma of the skin is often found with neurofibroma, lipoma or chondroma. Therefore, Dean and McCarthy believe that a tentative diagnosis of hemangioma of a viscus is warranted when a patient who has hemangioma of unusual extent suddenly experiences bleeding of uncertain origin.

Swan and Balme report a case of renal hemangioma and analyze 26 other cases of the lesion as reported in the literature. They found that in 80 per cent of the cases symptoms occurred before the patient reached the age of 40. The differential diagnosis was often difficult. Renal tuberculosis usually can be eliminated in the absence of dysuria, frequency of urination and pyuria. The absence of acid-fast bacilli and the presence of a normal cystoscopic picture of the mucosa of the bladder also aid in excluding this disease. Hemorrhagic nephritis is ruled out by the presence of unilateral bleeding and the absence of casts. Carcinoma of the kidney is rare before the age of 40, while renal hemangioma occurs most often before that age. Tumor of the kidney usually causes some pyelographic deformity, while in most cases hemangioma does not. In more than 40 per cent of the 27 reported cases the passage of blood

10. Dean, A. L., and McCarthy, W. D.: Hemangioma of the Kidney Associated with Multiple Hemangiomas, *Tr. Am. A. Genito-Urin. Surgeons* **33**:1-9, 1940.

clots from hemangioma caused lumbar pain or unilateral pain low in the abdomen similar to that caused by calculi in passage. However, renal and ureteral calculi, if present, can usually be found by roentgen study.

The principal symptom of renal hemangioma is hematuria. It is characteristically intermittent for days or weeks. Finally, it culminates in such profuse bleeding that an immediate operation is necessary to save the life of the patient. At operation the diseased kidney looks normal because the majority of the lesions are small and are situated beneath the epithelium of the pelvis, never involving the outer surface of the kidney. It is essential, therefore, to identify the diseased kidney by urologic methods before operation.

Bumpus,¹¹ in discussing the paper by Dean and McCarthy, reports 2 instances of hemangioma. One involved a patient he had treated in his student days in the Children's Hospital in Boston; it was a typical instance of poliomyelitis. No one had been able to make an accurate diagnosis until Dr. Harvey Cushing examined the child, found a small hemangioma on the face and said the child probably had hemangioma of the spinal cord. He operated the next week and found hemangioma of the spinal cord.

The second instance concerned a boy who had had hematuria first when he was 7 years of age. The bleeding had been extremely profuse and had required transfusion of blood a number of times. Bumpus followed the course of this patient at the Los Angeles County Hospital for two years. A 10 per cent solution of silver nitrate was injected to stop the bleeding. The boy tolerated this solution. There was one small filling defect in the lower calix of the left kidney, and it never changed. This patient was 14 years of age at the time of the discussion. Bumpus finally had to remove the lesion; no other hemangioma was detected in any other part of the body.

Froug¹² reviews 6 cases of liposarcoma of the kidney from the literature and adds 1 new case. His case is the fourth in which tuberculous sclerosis has been associated with this lesion. Perirenal insufflation of air with intravenous pyelography was a valuable aid in distinguishing renal tumor from perirenal tumor.

Calculi.—Boyd¹³ reports on 4 patients with multiple small phosphatic stones and sand in the kidneys; 3 of them had poliomyelitis with rather

11. Bumpus, H. C., in discussion on papers of Dean and McCarthy,¹⁰ *Hematuria and Strumia*,²⁰ Bugbee⁸ and Wishard,⁷⁴ *Tr. Am. A. Genito-Urin. Surgeons* **33**: 57-60, 1940.

12. Froug, C.: *Liposarcoma of the Kidney: Review of the Literature and Case Reports*, *J. Urol.* **45**:290-295 (March) 1941.

13. Boyd, M. L.: *The Formation of Renal Calculi in Bedridden Patients*, *Tr. Am. A. Genito-Urin. Surgeons* **33**:257-263, 1940.

extensive paralysis, and the fourth had suffered from a fractured femur which would not unite satisfactorily. The fourth patient had many rather small renal stones, all of which were passed after he had drunk large quantities of water and had lain three or four hours a day on his abdomen. One large stone would not pass through the ureter.

Multiple phosphatic stones probably can form in the kidney solely as a result of phosphaturia and lack of proper drainage due to position.

Naturally, all the other factors known to cause formation of renal stone may, and no doubt often do, exist in bedridden patients, and every precaution to prevent such formation, including drainage by posture, should always be taken.

Higgins,¹⁴ in discussing Boyd's article, states that many factors are associated with the formation of stones in bedridden patients, about whom several interesting observations can be made.

First, the prolonged immobilization of the patients is accompanied by increased excretion of calcium. This can be demonstrated in a roentgenogram of the bones of the body.

Second, when a patient enters the hospital and is first immobilized, the reaction of the urine frequently is acid. After a short period of immobilization, the reaction of the urine invariably becomes alkaline. This change is influenced largely by the diet of the patient. An examination of the trays of patients who have been bedridden for an extensive period of time invariably will reveal that they eat more vegetables, are usually given large glasses of orange juice daily and only nibble at meat or those foods with an acid-ash base.

Third, constipation tends to develop among all these patients, and they are given large doses of peristaltic agents and liquid petrolatum. Higgins says that he has clinically demonstrated that if a patient is deficient in vitamin A and is given large doses of liquid petrolatum, he does not absorb the vitamin A concentrates. It is almost impossible to secure a normal biophotometric reading until the use of liquid petrolatum is discontinued.

Fourth, repeated catheterization of patients with injuries of the spinal cord eventually will introduce infection into the urinary tract. If a urea-splitting organism is introduced, the urine becomes strongly alkaline, and the pH is elevated to a point at which precipitation of alkaline salts occurs.

Fifth, prolonged immobilization may foster stasis in the kidney.

Several steps may be taken, therefore, to prevent the formation of stones in bedridden patients, such as: (1) acidification of the urine by dietary means, that is, the inclusion of the acid-ash diet or acidifying

14. Higgins, C. C., in discussion on papers of Livermore,⁴¹ Davis and Nesbit⁴² and Boyd,¹³ *Tr. Am. A. Genito-Urin. Surgeons* **33**:264-267, 1940.

agents and the omission, of course, of ammonium salts if a urea-splitting organism is present; (2) avoidance of the use of alkaline urinary antiseptic agents; (3) forcing of fluids; (4) changing of the patient's position in bed at frequent intervals; (5) administration of one of the various concentrates of vitamin A; (6) avoidance of administration of liquid petrolatum for extended periods; (7) careful observation of diet, so that if sufficient proteins are not taken, additional acidifying agents can be prescribed, and (8) exercise of extreme caution in catheterization to minimize the possibility of the introduction of organisms into the bladder.

Cases have been reported of the development in bedridden patients of stones which dissolved spontaneously when the patients became active again. Higgins says that he has on record a series of 9 patients in whom during the period of immobilization stones formed which were dissolved completely by means of dietary management.

Gutierrez¹⁵ reported a case in which calculous pyonephrosis afflicting a boy 13 years of age was complicated by vesicoureterorenal reflux. The boy was cured by nephroureterectomy. This patient had been suffering from pyuria and occasional hematuria for the previous three years. Urographic study revealed a functionless state of the right kidney, calculous pyonephrosis and evidence of hydroureter and reflux, conditions rarely found together. Vesicoureteral reflux of urine is in itself a relatively infrequent finding. It is caused as a rule by congenital malformation but often by infection; both, in fact, may play a part in its causation, as they did in the present instance.

The necessity for complete urologic study of pyuria among children is pointed out. When the kidney is functionless and the ureter is diseased, it is important to remove both the kidney and the ureter, provided the function of the opposite kidney is good. According to the conditions that may be present, combined nephroureterectomy or ureteronephrectomy should be performed. Gutierrez says that he prefers combined ureteronephrectomy. However, for a young patient without much adipose tissue whose ureter is not so obviously diseased or dilated and whose kidney merits surgical exploration in the hope that it can be saved by a conservative procedure, although it has no function as revealed in the excretory urogram, exposure of the kidney should be done first and then aseptic nephroureterectomy should be carried out. To leave an infected, dilated or obstructed ureter in its place is to invite complications. When vesicoureteral reflux is present, if the ureter is not removed with the kidney, lumbar urinary fistula or other complications almost certainly will develop.

15. Gutierrez, R.: Calculous Pyonephrosis in a Boy Thirteen Years of Age. Complicated with Vesico-Uretero-Renal Reflux, Cured by Nephroureterectomy. *Urol. & Cutan. Rev.* 45:117-120 (Feb.) 1941.

In cases in which intravenous urograms disclose a functionless calculous pyonephrotic kidney, if there is assurance of normal function in the kidney of the opposite side and if a good cystogram shows the condition of the bladder, routine cystoscopic examination, and the making of retrograde pyelograms may not be necessary. This is the more so if roentgenograms show that a calculus is impacted at the ureteropelvic junction of the offending kidney and if no excretion can be obtained from the same kidney in the excretory urograms. In such a case, complete blocking produced by stone is obvious and there is no need to distend the renal pelvis by injecting the ureter from below. Among children intravenous urography together with the making of a cystogram or a cystourethrogram is a much simpler procedure than cystoscopy. The latter should be done only if absolutely indicated.

Hydronephrosis.—Shupe¹⁶ states that conservative surgical treatment of hydronephrosis may be attempted in the presence of all degrees of ureteropelvic obstruction, whether infection is present or absent and even if the function of the kidney is much diminished. Postoperative drainage of the pelvis is necessary whether infection is present or not. By means of conservative plastic surgery, patients may still retain both kidneys and be relieved of pain and infection for periods of three to six years and possibly permanently.

Quinby,¹⁷ in discussing Shupe's article on conservative surgery for renal pelvic obstruction, calls attention to the fact that the blood supply of the upper end of the normal ureter (that portion adjacent to the renal pelvis) is just as ample as the blood supply to any other part of the ureter. Although there has been no hesitancy on the part of surgeons to carry out plastic procedures on the lower end of the ureter, there seems to be still in the minds of many surgeons a hesitancy to rely on the natural blood supply of the upper end of the ureter to permit quick healing if the ureter is severed from the renal pelvis. Quinby's own experience in operations in which the ureter was entirely divided from the renal pelvis is now sufficient to demonstrate this point, namely, that the blood supply of the normal ureter is adequate to allow perfectly smooth healing after complete division followed by the reimplantation of the severed end. In a good many cases of this type there has been antecedent infection which may have died out by the time of operation, so that even though the tissues may be sterile, definite formation of scar tissue is left at that area. When this exists, it does not seem logical to attempt a plastic operation through the old scar, because, regardless of

16. Shupe, T. P.: Conservative Surgery in Renal Pelvic Obstruction, *Tr. Am. A. Genito-Urin. Surgeons* **33**:101-114, 1940.

17. Quinby, W. C., in discussion on papers of Colby²¹ and Shupe,¹⁶ *Tr. Am. A. Genito-Urin. Surgeons* **33**:115-121, 1940.

what may happen after the operation, healing can be accompanied only by further formation of scar tissue.

For these reasons Quinby chooses to avoid such an area entirely in the attack on the obstruction. He has therefore strongly advocated complete severance of the ureter followed by implantation of it into whatever other portion of the pelvis seems advantageous from a mechanical point of view. True, the whole pelvic wall in instances of considerable dilatation will exhibit hypertrophy in some degree, but it is not scarred. In cases in which free transplantation of the upper end of the ureter has been made into some other portion of the pelvis, the operation is much simpler and more logical than any of the rather complicated plastic procedures.

Pseudohydronephrosis.—Johnson and Smith¹⁸ reported a case of perirenal pseudohydronephrosis with calcification. A woman 41 years old entered the hospital complaining of a symptomless mass in the left side of the abdomen. It extended from the costal margin to below the umbilicus, filled the flank and extended to the midline anteriorly. Thirty-seven years before, a wagon had passed over her abdomen and flank; from this injury she had finally recovered. Results of a physical examination were negative except for this large, nontender, firm, nodular, rounded and immobile tumor.

Complete urologic study revealed a calcified multicystic mass in the vicinity of the left kidney. The left ureteral catheter was obstructed at 20 cm. The contrast medium would not pass above this point, and urine was not obtained.

At operation, a multilocular calcified cyst containing amber-colored fluid was found directly under the transversus abdominis muscle. It communicated with the pelvis of an atrophic hydronephrotic kidney. The cyst and the remnant of the kidney were removed.

Perirenal pseudohydronephrosis can develop after renal trauma only when complete laceration through the renal parenchyma, as well as ureteral obstruction, obtains. This injury allows the extravasation of both blood and urine into the perinephric space, limited by the perinephric fat and Gerota's capsule. After bleeding ceases, the urine continues to pass out through the renal wound because of the ureteral block, which will not allow the parenchymal tear to heal, and progressive hydronephrosis is the rule.

In the presence of the urine the perirenal fat becomes fibrosed and finally hyalinized. For this reason perirenal fat is not found between these cysts and the transversus abdominis muscle, and these cysts are not lined by epithelium.

18. Johnson, C. M., and Smith, D. R.: Calcified Perirenal Pseudohydronephrosis, *J. Urol.* 45:152-164 (Feb.) 1941.

Pathologic calcification may occur in any devitalized tissue in the body, and it is not surprising that it should occur in the hyalinized avascular wall of the cyst. In this regard, however, this case is unique in the literature. Other cases of calcification about the kidney after trauma have been published, but proof is lacking as to the exact condition present. Certain intrarenal lesions lead to pathologic calcification, and the walls of solitary cysts not uncommonly contain calcium, but complete urologic investigation easily distinguishes these lesions from calcified perirenal pseudohydronephrosis.

Surgical excision of these calcified tumors is not advisable unless symptoms are bothersome, because of the marked adherence of the walls of such tumors to the peritoneum, muscle and rib cage.

Pyelonephritis.—Prather and Sewall¹⁹ discuss the relation of pyelonephritis to toxemia of pregnancy.

The data for their paper are based on the observations and records of 72 patients who had pyelonephritis and were pregnant in the period from 1930 to 1939. Records of only those patients who were pregnant one or more times subsequent to the pregnancy complicated by pyelonephritis are used. Of the 72 patients, 42, or 58.3 per cent, were primiparas; 30, or 41.7 per cent, were multiparas. Seventy had pyelonephritis during pregnancy; 2 had acute pyelonephritis immediately after delivery, while they were still in the hospital. Forty-three, or approximately 60 per cent, were in a febrile phase while they were in the hospital, leaving 29, or 40 per cent, in an afebrile subacute stage at the time of observation.

The records of these patients suggest a history of pyelonephritis among 16.6 per cent; half of these had the disease during a previous pregnancy, and the remaining half had had pyelonephritis before the onset of any pregnancy.

Roentgen data were obtained concerning 55 patients, 26 of whom had had intravenous pyelographic study and 29 of whom had had retrograde roentgen study. The dilatation of the ureters and the pelvis and the ureteral kinks were not extraordinary to any one familiar with urologic changes during pregnancy. The renal and ureteral dilatation in the subsequent pregnancy never exceeded that encountered during the time of the first occurrence of pyelonephritis, irrespective of whether the subsequent pregnancy was normal or complicated by recurrent pyelonephritis or toxemia. In general, patients with toxemia appear to have less ureteral and pelvic distortion (as revealed by intravenous pyelograms) than normal women.

Of the 72 patients with pyelonephritis, 47, or 65.28 per cent, completed a normal pregnancy at a later date. The interval between the

19. Prather, G. C., and Sewall, W.: *Relation of Pyelonephritis in Toxemias of Pregnancy*, Surg., Gynec. & Obst. **72**:781-786 (April) 1941.

pyelonephritis that had arisen during pregnancy and the normal pregnancy varied between one and nine years, the average interval being three and sixty-two hundredths years. Frequent recordings showed the blood pressure to be normal during the subsequent pregnancy in all 47 cases. In 34 of the patients blood pressure during the normal later pregnancy was about the same as it had been during the pregnancy that was complicated by pyelonephritis; in 13 patients it averaged lower than it has been during the uncomplicated pregnancy.

Of the 72 patients who later returned pregnant to the hospital, 9, or 12.5 per cent, were afflicted with toxemia.

Prather and Sewall conclude that pyelonephritis is not a cause of toxemia of pregnancy.

Hemorrhagic Cysts.—Herman and Strumia,²⁰ discussing primary hemorrhagic cysts of the kidney, state that these cysts are rare in surgical practice. Their series was made up of 6 cases in which the patients were subjected to operation. The cysts were of the simple retention type, and 3 could be classified as primarily hemorrhagic. In each of these cases the symptoms and the pyelographic observations led to the erroneous diagnosis of neoplasm. Either type of cyst may come to the attention of the surgeon because of symptoms arising from a complicating lesion, such as stone or inflammation, but in the present series all the patients had gross renal hematuria, accompanied in 1 case by pain. Hemorrhage in a case of simple retention cyst of the kidney probably is caused by rupture of distended veins in the walls of certain calices, the distention arising as a result of interference with the circulation. Certain cysts of the type under discussion may be treated successfully by segmental resection. This was the means employed in 1 case of simple cyst in the series reported by Herman and Strumia. However, the occurrence of gross bleeding from a kidney presenting somewhat diminished function and pyelographic distortion highly suggestive of neoplasm frequently leads the surgeon to remove the kidney, notwithstanding the benign appearance of the visible portions of the cyst.

Herman and Strumia summarize their observations by saying that primary hemorrhagic cysts are of variable causation and mechanism, as reflected in the great variety of pathologic observations which are made, and that although they are dependent on diseased blood vessels the predisposing lesion is not necessarily aneurysmal.

Tuberculosis.—Colby²¹ states that patients suffering from renal tuberculosis are so benefited by treatment in a sanatorium before opera-

20. Herman, L., and Strumia, M.: Primary Hemorrhagic Cysts of the Kidney. *Tr. Am. A. Genito-Urin. Surgeons* 33:11-23, 1940.

21. Colby, F. H.: Renal Tuberculosis and Sanatorium Care. *Tr. Am. A. Genito-Urin. Surgeons* 33:95-99, 1940.

tion that such treatment should be a part of the routine care. Operation is seldom advisable until the patient shows evidence of increased resistance to the disease. This service is rendered best by institutions in which care is devoted to extrapulmonary tuberculosis, but few communities have hospitals of this character.

Renal and genital lesions complicate tuberculosis of bone more frequently than is generally supposed, and constant albuminuria is an early indication that the kidney may be involved. At the Lakeville State Sanatorium, Middleboro, Mass., the inoculation of guinea pigs has been a more reliable laboratory procedure for the detection of tuberculosis than the taking of material for cultures.

Baggenstoss²² states that healed miliary tubercles of the kidney were found incidentally at necropsy in 9 cases. Similar miliary tubercles with definite evidence of regression but slight histologic evidence of activity were found in 6 additional cases. In none of these cases was there any clinical evidence of either renal or pulmonary tuberculosis. These cases add to the evidence that renal tuberculosis heals when circumstances are favorable. It is probable that healed tubercles of this type occur more frequently than the small number of cases reported indicates.

Keyes²³ reports 6 cases in which cutaneous ureterostomy (in 1, bilateral) was performed for tuberculosis. In these cases the operations of nephrectomy and contralateral ureterostomy were performed: in 1 case they were performed simultaneously; in 1 case ureterostomy was done before nephrectomy; in 4 cases it was done after nephrectomy, at intervals of two, four, five and six years.

At the time of Keyes's report (1940), 3 patients had given no suggestion of tuberculosis in the kidney or ureter since ureterostomy. These patients (except 1 who needed meatomy) had made no complaint and needed no attention to the ureter during a postoperative interval of three (in 1 case) to nineteen (in 2 cases) years. They did not need a catheter. Two of them kept themselves dry by night as well as by day, and the third, a surgeon, was "too much enamoured by his homemade apparatus to bother about his wet nights." Three patients were well and free from the odor from the urine. One married since undergoing ureterostomy; 1 bore a child, something she had previously been deemed incapable of doing.

The 3 patients who had tuberculosis of the remaining kidney were wearing an indwelling catheter at the time of Keyes's writing. The 2 who were followed had phosphatic stone within three years after ureter-

22. Baggenstoss, A. H.: Healed Tuberculosis of the Kidney, *J. Urol.* **45**:165-175 (Feb.) 1941.

23. Keyes, E. L.: Cutaneous Ureterostomy for the Relief of Intractable Bladder Tuberculosis After Nephrectomy, *Tr. Am. A. Genito-Urin. Surgeons* **33**:169-174, 1940.

ostomy. Yet, perhaps because there was good ureteral drainage, the progress of the renal lesions seemed slow, and other tuberculous lesions tended to subside. One of these patients died thirteen years after ureterostomy.

This report justifies no conclusion other than that cutaneous ureterostomy may bring long life to the patient tortured by a tuberculous bladder.

Rupture.—On the basis of experimentation with animals and clinical experience with human beings, Lowsley and Menning²⁴ conclude that early operation, evacuation of blood clots and production of hemostasis by means of pieces of fat held in place by ribbon gut fixed in the capsule will be followed by less destruction than failure to treat renal traumatism. Any patient who has a history of trauma and who has had hematuria for more than twenty-four hours should have the benefit of an exploratory operation, because such a procedure is now considered to be much more conservative than hopeful waiting.

Engel²⁵ states that Lowsley and Menning have departed from the usual conservatism in advocating exploratory operation in every case of suspected rupture of the kidney in which the bleeding persists for more than twenty-four hours. Their own statistics permit question of the wisdom of this attitude, for of 36 patients seen by them since 1920, 17 were operated on, with 6 deaths, a mortality rate of 35 per cent; whereas among 19 patients not operated on there was only 1 death, a mortality rate of only 5 per cent. Engel favors a policy of watchful waiting for traumatic rupture of the kidney, especially the subcapsular type, reserving operation for those patients who have severe extracapsular hemorrhage or for the occasional patient for whom watchful waiting must be abandoned because a sudden turn of events threatens his life. Of 17 patients seen in Engel's clinic since 1922, only 2 were operated on; both underwent nephrectomy.

Wood²⁶ states that the main problem in a case of injury to the kidney is that of determining the extent of the injury and the time at which to operate. A considerable number of patients who suffer trauma to the kidney will recover after conservative treatment. For this reason Wood questions whether or not all patients who have hematuria of no more than twenty-four hours' duration should be subjected to operation. The patients who need immediate operation are those who have severely injured kidneys, which are usually completely ruptured. The main

24. Lowsley, O. S., and Menning, J. H.: Treatment of Rupture of the Kidney. *J. Urol.* **45**:253-271 (March) 1941.

25. Engel, W. J., in discussion on papers of Lowsley and Menning²⁴. McKenna and Kiefer,² *J. Urol.* **45**:282-289 (March) 1941.

26. Wood, A. H., in discussion on papers of Lowsley and Menning²⁴. McKenna and Kiefer,² *J. Urol.* **45**:282-289 (March) 1941.

difficulty is to determine the time at which to operate on these patients. In Wood's experience, they do better if allowed to recover from the immediate shock with supportive treatment. If operation is carried out, it should be deferred, if possible, for at least three or four days.

URETER

Injuries.—Smith and Smith²⁷ discuss transureteroureteral retroperitoneal anastomosis in man. They report 2 cases in which the operation was successful.

Their procedure is as follows: Prior to operation a ureteral catheter is passed up the good ureter for a reason that will presently be made clear. An incision is made in the midline below the umbilicus, and the abdomen is opened in the usual manner. The patient is placed in the Trendelenburg position, the intestines are packed off, and the ureters are identified. An incision is then made in the posterior parietal peritoneum over each ureter, a short distance above the brim of the pelvis. The ureter on the injured side is freed over a distance sufficient to permit it to swing freely over to the opposite ureter. The injured ureter is doubly ligated with catgut and divided. Then, with a Kelly clamp, a tunnel is made under the posterior parietal peritoneum. The ligated ureter is then drawn through the tunnel and brought to lie alongside the noninjured ureter in such a manner that no tension is present. Anchor sutures of no. 2 chromic catgut are placed approximating the two ureters for a distance of 2 or 3 cm. Longitudinal incisions are made in each ureter along the borders of approximation. The posterior layer of the anastomosis is then closed with interrupted sutures of no. 000 chromic catgut. Once the posterior layer is laid, the catheter which was inserted before operation is drawn down until the tip can be grasped and brought out through the anastomosis. Two no. 7 or no. 8 French ureteral catheters are fixed to the tip of the catheter. The original catheter is then drawn out, so that the two catheters are carried with it until these can be grasped from the outside. The proximal end of the one catheter is placed into the pelvis of the normal kidney, and that of the other catheter is inserted into the renal pelvis of the injured side. The purpose of this procedure is to divert as far as possible the flow of urine over the site of anastomosis. After this, the anterior suture line is put in place, completing the anastomosis. At this point sutures are placed in both ureters distally and proximally to the anastomosis and are sutured to the fascia of the psoas muscle. This is done to relieve further any tension that may be exerted on the anastomosis. A stab wound is made in the side, and a soft rubber drain is

27. Smith, P. G., and Smith, D. P.: Ureteral Injuries and Their Management, *Tr. Am. A. Genito-Urin. Surgeons* 33:175-183, 1940.

brought down to, but not in contact with, the anastomosis. The openings in the posterior parietal peritoneum are closed with continuous sutures of catgut. The abdomen is then closed in the usual manner. The ureteral catheters are fastened to the inner aspects of the patient's thighs and are left in place for four or five days.

Stone.—Bergman²⁸ reports 9 cases of vaginal ureterolithotomy; in 8 of these the operation was successful.

He states that stones lodged in the vicinity of the ureterovesical juncture may be extremely difficult to remove; this is indicated by the number of procedures which have been advocated for attack on calculi lodged in this region. Bergman cites Lower's statement that of the four avenues of approach to ureteral stones lodged within the pelvis, namely, the vesical, the rectal, the sacral and the vaginal, the latter has distinct advantage in that it is the simplest, easiest for the surgeon to utilize and least disturbing to the patient. The vaginal route has a notable superiority over the abdominal route, particularly when adiposity and adhesions are marked. Anatomically, the approach from below is not only more logical but also simpler, and it is accompanied by a minimal degree of shock. Drainage is dependent, and the possibility of development of external incisional hernia is excluded. Morris is quoted as saying that the lower part of the ureter passes

from $\frac{1}{3}$ to $\frac{1}{2}$ inch above and to the outer side of the lateral fornix of the vagina, crossing beneath the broad ligament, and uterine artery at the side of the neck of the uterus, from which it is separated by loose connective tissue. The distance between the cervix uteri and the ureter is $\frac{3}{4}$ to 1 inch. The ureter terminates at the base of the bladder $1\frac{1}{4}$ inches from its fellow of the opposite side. It lies in front of the anterior vaginal wall, $\frac{1}{4}$ to $\frac{1}{2}$ inch below the anterior fornix.

Bergman states that he places the patient in the extreme lithotomy position. While the patient is under anesthesia, an attempt is made to palpate the stone through the vagina. If orientation is difficult, a catheter inserted in the ureter may serve as a guide. Flexible retractors are then placed into the vagina. The cervix is grasped with a tenaculum forceps and traction is exerted to gain better access to the stone by bringing the base of the bladder and ureter into the field.

The incision is transverse, usually 3 or 4 cm. long, and is made anterior and lateral to the cervix through the mucous membranes of the vagina; thus it is made directly over the stone, if the stone is palpable. The incision is further deepened with blunt dissection by forceps, and the finger then introduced should palpate the stone. To avoid serious bleeding it is important to remember that the uterine artery will be found above and medial to the ureter. The ureter is then grasped with an 8 inch (20 cm.) Babcock forceps placed above the calculus, if possible.

28. Bergman, R. T.: Vaginal Ureterolithotomy, *J. Urol.* **45**:176-185 (Feb.) 1941.

to prevent the calculus slipping up the ureter. With the ureter thus exposed, a longitudinal incision is made through the wall of the ureter and the calculus removed. Fine chromic catgut is used to suture the ureteral incision, and the vaginal incision is left open for drainage.

Unless the calculus is impacted, it may slip up the ureter beyond reach when removal is attempted. This has occurred in 5 of Bergman's cases. In 3 of these cases the Johnson basket dislodger was successfully utilized by passing it through the vaginoureteral incision and engaging the stone, which was then easily removed from the dilated ureter.

The ureter is below and lateral to the uterine artery, so that dissection carried in a more lateral direction should avoid injury to this vessel.

Postoperative ureteral drainage by catheter has been used in most of Bergman's cases but has not seemed to diminish appreciably the transient postoperative leakage of urine through the incisional orifice. In his series, the shortest duration of urinary leakage through the incision was four days, and the longest period (the patient had experienced severe hemorrhage) was one in which drainage persisted for ten weeks before the incision closed spontaneously. In most of the cases, drainage endured from one to three weeks after surgical intervention.

Transplantation.—Stevens²⁹ states that reports concerning 38 patients who have survived ureterointestinal implantation for nonmalignant conditions are to be found in the literature; 11 of these patients had survived for more than twenty years. Two patients whose cases are recorded in Stevens' paper bring the figure for those reported living more than twenty years to 13. The number of patients who have lived this long after the operation probably is much larger but unrecorded.

All but 1 of the 38 patients referred to were victims of exstrophism of the bladder.

A report is given concerning a man living for more than forty-three years after operation, performed by the late Dr. George R. Fowler.

Brief summaries of the conditions of the 7 patients whose ureters were placed in their bowels on account of incontinence referable to non-malignant conditions, are appended to Stevens' report: 2 died after six years of life; the others were living four to twenty-nine years after operation at the time of Stevens' report.

BLADDER

Tumor.—Watson and Herger³⁰ present the methods of treatment and the results in 445 cases of tumor of the bladder. An attempt was

29. Stevens, A. R.: Longevity Following Uretero-Intestinal Anastomosis, with Report of Cases, *Tr. Am. A. Genito-Urin. Surgeons* **33**:157-167, 1940.

30. Watson, E. M., and Herger, C. C.: Carcinoma of the Bladder: A Correlation of the Pathological and Clinical Data as a Basis for Treatment, *J. Urol.* **45**: 331-336 (March) 1941.

made to correlate the clinical picture and the pathologic observations, so that a basis for choice of treatment might thereby be established. Operation, radiation therapy and electrocoagulation were used either alone or in various combinations. Statistics are presented for two five year groups. In the first group, 28 per cent of the patients with papillary tumor remained well for more than five years, while 12 per cent of those with solid infiltrating tumor remained well for more than five years. In the second five year group, Watson and Herger were able to obtain disappearance of papillary tumor in 43 per cent of the patients for periods of from one to four years, although of the patients with nonpapillary solid infiltrating tumors only 10 per cent remained alive and well for periods of from one to four years. It is their opinion that results in the second group will be improved, partly because of advances in the technics of operation and radiation therapy and partly because of a better adaptation of the methods of treatment employed in the different clinical and pathologic groups.

Colby³¹ states that tumor of the bladder treated with 1,000,000 volts of external radiation, constant potential, has responded better than that treated with lower voltage. Well marked regression of the tumor has occurred in about half the cases in which this method of treatment has been employed, and at least temporary disappearance of the tumor has been secured in about a third of the cases. In the present experimental stage, it is doubtful whether this agent is curative, and it should not be regarded as a substitute for surgical treatment. Symptoms, such as bleeding and painful and frequent urination, were relieved in about half the cases.

Leukoplakia.—Thompson and Stein³² report a series of 34 cases of leukoplakia of the urinary bladder. They observed that although in most instances there were no cardinal symptoms of leukoplakia, the patients complained of suprapubic pain and tenderness unassociated with voiding. In most cases the diagnosis was verified by biopsy, and the authors stress the necessity of such an examination. The disease is more common among men and is most frequently situated around the trigone of the bladder. In every case of leukoplakia, associated pyuria and excretion of cocci were observed. Treatment consisted of fulguration of the leukoplakial portions either by suprapubic or cystoscopic approach. The latter method was considered preferable because the extent of the leukoplakial lesion can be recognized with a reasonable approximation of accuracy with the cystoscope, while it is comparatively difficult to delineate the lesion with the unaided eye through a suprapubic incision.

31. Colby, F. H.: Evaluation of the Supervoltage Treatment of Bladder Tumors. *J. Urol.* **45**:337-341 (March) 1941.

32. Thompson, G. J., and Stein, J. J.: Leukoplakia of the Urinary Bladder: A Report of Thirty-Four Clinical Cases, *J. Urol.* **44**:639-649 (Nov.) 1940.

Thompson and Stein employ an interesting method of treating the lesions: They first fulgurate a line around the periphery of the entire lesion and then proceed with superficial fulguration within this zone. This is necessary because repeated distention of the bladder produces a fading of the margins of the lesion. The results of this treatment have been satisfactory.

The combination of leukoplakia and carcinoma was found in only 2 instances in this series. The authors point out that leukoplakia occurs in the stratum corneum, the cells of which are dead. These cells have lost all power to react to stimuli, and it is impossible for a malignant process to develop within the cornified or leukoplakial region.

Obstruction of the Neck of the Bladder.—Trabucco³³ made a comparative study of pathologic conditions of the neck of the bladder in men and women. Although such pathologic aspects have received recognition and close attention in men from time immemorial, it must be admitted that the study of diseases of the neck of the bladder in women is still in its infancy and that the causes of such diseases too frequently remain unrecognized.

In women acute retention of urine seems to predominate at the outset, and retention becomes irreducible, requiring permanent use of a catheter and surgical intervention. In men, on the contrary, the first symptom is dysuria, signalized by retardation of the urinary stream. This is premonitory of retention. Trabucco thought that dysuria is present in both men and women but that in the latter, for obvious reasons, it is more difficult to establish the fact that it is present.

The embryonic anatomy of the two sexes is reviewed, and it is pointed out that in women the muscle of the vesical neck is not so evident as it is in men; it is broader and is directed downward, occupying nearly half the urethra in women, resulting in a certain anatomic difference of some importance.

In men two basic types of the disease may exist: (1) the circular, which embraces the entire contour of the neck, and (2) that which is localized in the so-called lower lip and is confined there. The former is chiefly traumatic, but occasionally it is congenital. The second type is again subdivided into fibrous and glandular changes. The fibrous subtype may be congenital yet may not reveal itself until senile changes of an inflammatory nature bring it to light. Acquired sclerosis of the so-called lower lip of the neck of the bladder, which is much more common than is supposed, is referable especially to prostatitis and seminal vesiculitis caused by one or another infective agent. The glandular type of change in the lower lip of the neck of the bladder in

33. Trabucco, A.: Estudio comparativo de la patología del cuello vesical en el hombre y en la mujer, *Rev. argent. de urol.* 9:355-361 (July-Aug.) 1940.

men is due to glandular hypertrophy. Home's lobe above the neck of the bladder in the region of the trigone and the subcervical glands of Albarran, which ordinarily remain in a state of latency, may undergo endocrine or other changes which cause them to increase in size so that they exert pressure on the muscle of the vesical neck and gradually cause destruction of it. Likewise, inflammatory changes may lead to invasion and destruction of the muscular elements by connective tissue. Retention then results from lack of kinetic force in the lower lip due to destruction of the latter's motor portion.

In women it has been considered that changes in the neck of the bladder must be caused solely by inflammatory hyperplasia of connective tissue or by change of the musculature into fibrous tissue. Theoretically, in women the vesical neck and the subcervical part of the urethra have no glands. Numerous works and histologic studies have seemed to prove this. The shortness of the urethra in women and its close proximity to infected zones readily account for the frequency with which the neck of the bladder becomes inflamed, especially among women of advanced age. Nevertheless, Trabucco recently encountered a young woman in whom retention of urine demonstrably was caused by typical glandular hypertrophy of elements situated in the lower lip of the neck of the bladder, an observation confirmed by histologic study.

Trabucco points out the importance of this observation. It might be more nearly accurate to say, not that the female urethra contains no glands, but that it contains no visible glands. That glands have not been found does not prove that they do not exist. It must not be forgotten that in women the elements of the lower lip of the neck of the bladder are derived embryologically from a special formation similar to that in men and that in this formation there exist glands in a state of latency. Although normally these glands atrophy in the female, it is wholly possible that special endocrine changes affect some women so that these glands persist, leading to glandular hypertrophy comparable to the changes in men that produce various types of adenoma.

Stone.—Emmett³⁴ states that vesical calculi of the ordinary type may reach enormous proportions. Some stones have been reported which were so large that they filled the entire bony pelvis. It may be impossible to remove such a stone through the usual suprapubic incision unless the stone is first broken into smaller pieces. On the other hand, it is relatively uncommon to encounter large calculi of the jackstone type in the bladder. Most jackstone calculi vary from 0.5 to 2 cm. in diameter.

Emmett reports the following case of large stone: A man 60 years of age stated that for ten years he had suffered from moderate urinary

34. Emmett, J. L.: Unusually Large "Jackstone" in the Urinary Bladder: Removal by Litholapaxy, *Proc. Staff Meet., Mayo Clin.* 16:269-270 (April 23) 1941.

symptoms. Digital examination of the prostate gland through the rectum revealed enlargement, grade 2. Roentgenograms of the kidneys, the ureters and the bladder revealed the shadow of a stone in the left renal pelvis and the shadow of an unusually large jackstone calculus in the vesical region. Cystoscopic examination revealed a free jackstone calculus, 5 or 6 cm. in diameter, a diverticulum about 3 cm. in diameter arising from the lower part of the right lateral wall of the bladder and grade 2 enlargement of the lateral lobes of the prostate gland. With the patient under light spinal anesthesia, the stone was crushed with a lithotrite, and the fragments were evacuated. The stone was extremely hard. Some of the fragments washed into the diverticulum, and it was necessary to introduce the beak of the cystoscope into the diverticulum to remove them. A urethral catheter was left in place for drainage. Four days later, with the patient under light spinal anesthesia, the prostatic obstruction was removed by means of transurethral resection. Chemical analysis of the stone proved it to be calcium oxalate.

Crance³⁵ reported a case in which he removed a giant vesical calculus with obstetric forceps. He reviews other cases of giant calculi from the literature. Randall (1921) reported the largest one in both measurement and weight on record. The calculus weighed exactly 4 pounds (1.8 Kg.), with a longitudinal circumference of 48 cm. and a horizontal circumference of 40 cm. Anagnostidis (1937) reported a large vesical calculus; the measurements were 11 by 16 cm.; the weight was not given. Louca (1930) described a calculus that weighed 630 Gm., with a height of 9 cm., a length of 7 cm. and a circumference of 26 cm. Bride (1936) found a large vesical calculus, 112 Gm. in weight, with dimensions of 6.5 by 6.0 cm., which had occurred during pregnancy. Greenberg (1937) described a giant vesical calculus a little more than 1 pound (0.5 Kg.) in weight. Daland (1935) reported what probably is the second largest stone on record; he said that it was almost 2 pounds (0.9 Kg.) in weight.

In Crance's case, a man aged 74 years had a giant vesical calculus which was seen roentgenologically to fill the bony pelvis almost completely. With the patient under anesthesia induced by nitrogen monoxide and oxygen, a midline suprapubic incision was made, and the bladder was easily exposed without previous filling by catheter. The bladder was opened longitudinally for a distance of nearly 4 inches (10 cm.) because of the size of the stone. When the bladder was opened, a large white hard calculus was seen. An attempt was made to deliver the stone bimanually, but this procedure was quickly abandoned because of the trauma which possibly would result. Short obstetric

35. Crance, A. M.: Removal of a Giant Vesical Calculus with the Aid of Obstetrical Forceps, *J. Urol.* 45:327-330 (March) 1941.

forceps were then applied in the customary manner, from above downward with the concave curve upward. Once the stone had been engaged in the forceps and clearly freed from the wall of the bladder, delivery was begun in an upward forward motion, and then by careful side to side movement the stone was delivered with only moderate difficulty and without additional traumatization of the original incision in the bladder. The stone was $1\frac{1}{2}$ pounds (0.7 Kg.) in weight. Its perimeter was 35 by 29 cm.

Diverticulum.—Kimbrough³⁶ presents a study of the treatment of 30 patients suffering from diverticula of the bladder observed during a twelve year period. During this twelve year period 375 patients were treated by operative procedures for obstruction of the neck of the bladder. The incidence of diverticulosis was 8 per cent.

It is universally agreed that obstruction of the neck of the bladder, except for the rare congenital type, is essential to the formation of a diverticulum, the blowout effect described by Keyes. Hinman has advanced the idea that this reverse pressure may be supplied without definite changes in the neck of the bladder.

Prostatic hyperplasia with varying degrees of fibrosis and the formation of median bars accounted for obstruction in 22 cases in this series. Fibrosis of the neck of the bladder without apparent enlargement of the prostate was present in the remaining 8 cases.

Stricture of the urethra was a causative factor in 2 cases.

Twenty patients had single, and 10 had multiple, diverticula. In 3 cases the diverticula were situated at the fundus in the region of the attachment of the urachus; in 10, near the right ureteral orifice, and in 7, near the left ureteral orifice; in 9 cases the diverticula were multiple bilaterally.

The symptoms were those of prolonged obstruction at the neck of the bladder with the associated effects of infection. The intensity of the disturbance was in direct proportion to the extent and the severity of the cystitis.

The cystogram provides the most nearly accurate information concerning the size, the situation and the number of the diverticula.

In all cases of this series, a plan of treatment for the diverticulum was made and carried out prior to relief of the obstruction of the neck of the bladder. Six of the patients received no operative treatment for the removal of the sac.

Kimbrough believes that diverticula of a capacity greater than 50 cc. which do not empty on urination or those which carry troublesome infection should be removed. Capacity alone is not an indication for surgical

36. Kimbrough, J. C.: The Treatment of Bladder Diverticulum: Report of Thirty Cases, *J. Urol.* **45**:368-381 (March) 1941.

intervention. The amount of constriction at the neck and the severity of infection are important factors. In recent years, with the increase of standardization of transurethral resection for obstruction of the neck of the bladder, many diverticula have been left intact.

Kimbrough gives the general principles of the operative procedure: Adequate preparation should be carried out. Safe anesthesia should be employed, and if spinal anesthesia is used (which Kimbrough has found "the most satisfactory") not more than 100 mg. of procaine hydrochloride should be employed.

A midline suprapubic incision should be made with adequate mobilization of the bladder and without urinary contamination of adjacent tissues. Vasectomy prior to or at the time of the operation will prevent the annoying occurrence of epididymitis. Ureteral catheters should be inserted before an attempt is made to separate the sac. It is more satisfactory to carry out ureteral catheterization after the bladder is opened than to precede the operation with preliminary cystoscopy. The best method or combination of methods suitable for each case should be selected, the intravesical, the transvesical or the extravesical approach.

Adequate drainage of the extravesical space for five or six days is necessary except in the removal of small diverticula by the intravesical technic. Adequate closure of the wall of the bladder at the site of the excision of the sac should be done. Drainage after suprapubic cystostomy should be maintained until the obstruction of the vesical neck has been corrected.

An ample interval should be allowed between diverticulectomy and removal of the obstruction at the neck of the bladder. In Kimbrough's series the average time between operations was forty-seven days.

Fourteen of the 30 patients had prostatectomy performed for the relief of urinary obstruction. Thirteen of these were operated on by the suprapubic approach and 1 by the perineal approach.

Council³⁷ reports a new operative technic for the cure of diverticulum of the bladder. An inflated balloon inserted into the diverticulum and then distended serves as a guide and buffer, and the catheter serves as an excellent tractor. This method not only insures excellent exposure but also changes a difficult operation into a relatively simple one. Council is of the opinion that any diverticulum of the bladder can be removed by this simple procedure, provided the balloon fits the diverticulum snugly.

Ritter and Linder³⁸ discuss pseudopodial diverticula of the urinary bladder.

37. Council, W. A.: A New Technic for Diverticulectomy of the Bladder: A Preliminary Report, *J. Urol.* **45**:382-387 (March) 1941.

38. Ritter, J. S., and Linder, H.: Pseudopodial Diverticula of the Urinary Bladder, *Am. J. Surg.* **49**:364-367 (Aug.) 1940.

They report a case in which the bladder of a man aged 64 years was found by cystographic study to be contracted in size and to have an hourglass constriction in its midportion. Five diverticula arose from the upper and four from the lower half of the bladder. Four of those arising from the upper half were small and resembled the ordinary type of diverticulum. The fifth one was a large piriform diverticulum arising from the right side of the upper half of the urinary bladder and extending down into the femoral region through the obturator foramen muscle for 3 inches (7.6 cm.). Three of the four diverticula arising from the lower half of the bladder extended down into the right femoral region and the mid thigh. The fourth diverticulum extended down into the left femoral region and was divided into three parts by two constrictions. These diverticula ranged in shape from piriform to curvilinear sausage form to pseudopodial form and varied in size from 2 to 6 inches (5 to 15 cm.). Suprapubic cystotomy was performed, but the patient died a few days later. Permission for necropsy could not be obtained.

Periostitis.—Wheeler³⁹ reports 3 cases of what he believed to be acute Sudeck's atrophy of bone, not, as formerly called, periostitis pubis. He has been unable experimentally to produce periostitis of the pubis, although in a suprapubic operation he tried to include all the factors present in addition to injury of the periosteum. Because of the clinical picture and the roentgen observations, he believes this disease to have been acute atrophy of bone, a form of trophoneurosis. It is a self-limited disease which requires no surgical intervention.

PROSTATE GLAND

Surgical Procedures.—Dorman⁴⁰ states that prostatic resection is a satisfactory treatment for many types of obstruction of the prostate. In his series of cases, 84 per cent of all obstructing glands were treated by resection. Prostatic resection is the simplest and easiest way to relieve obstructive symptoms among more debilitated men and those suffering from advanced carcinoma. All urologists cannot become expert resectionists. However, urologists being trained at the present time should avail themselves of every opportunity to become proficient in the technic of resection. The importance of adequate equipment, of thorough preparation of each patient, of intelligent nursing care and of meticulous attention to the details of resection are stressed.

Livermore⁴¹ states that dysuria, frequency of urination and nocturia may follow resection, just as they may follow prostatectomy.

39. Wheeler, W. K.: Periostitis Pubes Following Suprapubic Cystostomy, *J. Urol.* **45**:467-475 (March) 1941.

40. Dorman, H. N.: Transurethral Prostatic Resection: A Statistical Study Based on Three Hundred Consecutive Cases, *J. Urol.* **45**:411-427 (March) 1941.

41. Livermore, G. R.: The Etiology of the Unsatisfactory Results Following Prostatic Resection, *Tr. Am. A. Genito-Urin. Surgeons* **33**:243-250, 1940.

Incontinence is a complication that can be prevented if the surgeon is careful never to cut proximally to the verumontanum. It may often be relieved by the application of fulguration in the internal meatus at the four points of the compass.

Late hemorrhage denotes malignant change or obstruction of the prostate gland.

Stricture is not caused by the coagulating or the cutting current. Stricture which follows resection is caused by passage of the large resectoscope without preceding this instrument with sounds gradually increasing in size.

Small tags and nodules which cause dysuria may be removed in the office with the resectoscope.

Resection in the hands of the best resectionists is still the operation of choice in all cases except those in which hypertrophy of the prostate gland is marked and extensive.

Creedy⁴² reports the results of transurethral resection done for 1,141 consecutive patients. More than one operation was done for 23.9 per cent of the patients. The total mortality rate for the series was 4.4 per cent, and the average total hospital stay was 16.2 days. The average amount of tissue removed increased from 3.3 Gm. per patient in 1930 to 33.8 Gm. in 1940. The amount of tissue removed exceeded 30 Gm. in 21.9 per cent of operations in the whole series and in 38.3 per cent of those done in 1940, even though operations for contractures and small prostate glands, as well as all operations done by men just beginning to specialize in urologic surgery were included in the calculations.

The stay in the hospital in Creedy's cases was longer than that reported by many others; this was largely due to the fact that nearly all the patients were penniless and came from out of the city; thus they had to be kept in the hospital until they were ready to go to their homes. Then, too, these figures referred to total hospitalization and not merely to the postoperative stay.

For patients with impaired renal function, if fever was present or if complications required treatment, preliminary drainage was employed, including cystostomy for those whose recovery of function with the indwelling catheter was poor, and in whom calculi were too large to admit of litholapaxy. On the other hand, patients who were in good condition and afebrile and whose renal function was normal had nothing to gain and everything to lose from preliminary drainage.

Spinal anesthesia was used for patients adjudged to be "good operative risks." Pentothal sodium was the agent employed for those with

⁴² Creedy, C. D.: Resection of the "Large" Prostate: Technique and Results, *J. Urol.* 45:715-720 (May) 1941.

hypertension, cardiac disease or impairment of renal function and for those who manifested undue apprehension. These included about half the patients.

A tight meatus was never dilated but was always cut. Any dilatation present disappeared within a few minutes, and the tight meatus rode with the sheath, so to speak, alternately compressing and stretching the urethra, sometimes with disastrous results. If narrowing was present behind the meatus or if the prostate gland was high and anterior, perineal urethrotomy was done.

The mode of attack on the gland itself was that advocated by Nesbit. Resection was begun at 12 o'clock and was deepened until the circular fibers of the capsule were seen. This detached the lateral lobes from one another and allowed them to fall backward and medially. Resection was then carried down between the right lateral lobe and the surgical capsule, so that the circular fibers were exposed almost, but not quite, to the verumontanum, until the lateral and median lobes were attached by a rather slender verticle pedicle. The same operation was then done on the left. Bleeding was controlled, and the pedunculated lateral and median lobes were excised last. The left index finger was then inserted into the rectum to push remnants into the lumen for resection with one hand and to verify the completeness of the section by palpation.

The Foley bag was used routinely, but traction was employed only when bleeding was troublesome because of a conviction that traction promotes incontinence.

After operation, irrigation was carried out at frequent intervals with a closed sterile system consisting of a reservoir, rubber tubing, a glass Y tube, a clamp and a urine bottle. The rubber tubing was used for only 1 patient and was then discarded. The bag was usually removed in three days. If the surgeon felt that the operation had been incomplete, it was repeated before voiding was permitted. If urination was difficult or if there was any appreciable amount of residual urine, resection was repeated.

Lowsley and Kilgore⁴³ report a method of total perineal prostatectomy designed to give greater protection to the vesical orifice. This procedure has been used by them in about 20 selected cases with excellent results. It is not indicated in cases in which carcinoma of the prostate gland is known or suspected to be present.

An arcuate incision is made about 1 inch (2.5 cm.) above the mucocutaneous junction of the anus so that the subcutaneous fat and the central tendon are exposed. The central tendon is then carefully incised down to the wall of the rectum, a procedure which allows the transversus perinei muscles to be retracted anteriorly. The rectum is

43. Lowsley, O. S., and Kilgore, R. N.: Total Perineal Prostatectomy: A Modification of a Previously Published Technique, *J. Urol.* **45**:196-201 (Feb.) 1941.

dissected away from the overlying areolar tissue until the rectourethralis muscle is exposed. This muscle is then incised or retracted laterally; this allows the rectum to be dissected away from the base of the prostate gland. A transverse incision is then made in the fascia covering the vesicles; this permits greater mobility of the gland later in the procedure. Then a transverse incision is made through the urethra at the apex of the prostate gland; the straight prostatic tractor is passed through the prostatic urethra into the bladder and opened. When the tractor is depressed downward, the anterior commissure is exposed; this is separated from the overlying tissues by blunt or sharp dissection, thus bringing into view the anterior margin of the vesical orifice. The anterior commissure is divided in the midline so that the vesical orifice and the prostatic urethra are exposed.

A transverse incision is then made in the prostatic urethra, just distal to the internal sphincter muscle. If the intrusion of the lateral lobe is so marked that the internal sphincter muscle cannot be visualized, a midline incision may be made through the floor of the urethra so that the posterior and middle lobes of the gland are divided. This incision bisects the entire prostate gland up to the vesical orifice, and by the exertion of lateral traction on either half of the gland, good vision can be obtained. The prostate gland may then be freed from the floor of the vesical orifice on both sides under direct vision and with a minimum of trauma to the internal sphincter. Bisection of the prostate gland allows good exposure of the seminal vesicles, so that these may be removed easily or clamped and ligated with the vasa deferentia and the accompanying blood vessels. Bleeding vessels are easily clamped and ligated.

A catheter is then passed through the urethra and into the bladder. The vesical sphincter and the membranous urethra are approximated with interrupted chromic catgut sutures.

Dougherty⁴⁴ made an analysis of 87 cases in which death occurred after operation on the prostate gland. Heart failure, hemorrhage, and sepsis were listed as causes of death in 79.5 per cent of these cases.

The significance of a "bad cardiac history" was emphasized. Death from hemorrhage occurred only among those patients who had undergone transurethral and suprapubic operation. Since the increase in appreciation of the blood supply of the prostate gland and the development of the bag hemostat, the number of deaths from the hemorrhage among patients who undergo transurethral procedures has been negligible. Careful postoperative observation by the surgeon and by specially trained nurses and early steps directed toward control of bleeding are of supreme importance in the treatment of this complication.

44. Dougherty, J. A.: *An Analysis of Causes of Death in Prostatectomy*, California & West. Med. 54:216-218 (April) 1941.

For patients who have elevated leukocyte counts, even in the presence of normal temperature and heart rate, otherwise elective operations should be postponed until the results of blood counts are more nearly normal.

Urethral manipulation of the hemostatic bag or of catheters is to be avoided in the presence of fever. This disturbing complication is probably controlled best by drainage by catheter, rest in bed, forced administration of fluids and the use of urinary antiseptic agents.

When spinal anesthesia is used, an adequate dosage of procaine hydrochloride is suggested. Smaller doses may require reenforcement of anesthesia with ether, and this constitutes an added risk.

The preoperative making of pyelograms by the intravenous technic is advised as a means of increasing the sum total of knowledge of the patient's operability and probable postoperative course.

The chief factors in lowering the mortality rate for surgical procedures on the prostate gland are the instant recognition and the immediate treatment of complications.

Vest,⁴⁵ discussing the mortality rate accompanying surgical intervention on the prostate gland, gives the results of treatment in a consecutive series of 410 patients who were admitted to the public ward service of the Brady Urological Institute of the Johns Hopkins Hospital, Baltimore. Operative procedures for the relief of prostatic obstruction were carried out on 365 of these patients with only 6 deaths—a mortality rate of 1.6 per cent. All the patients were operated on by members of the resident staff who were receiving urologic and surgical training. The selection of the type of treatment, whether prostatectomy or transurethral resection, and the carrying-out of the necessary procedures and operations were entirely the responsibility of the residents. The condition of these patients on admission was similar to that of patients in other public ward services. Patients with prostatic obstruction were not refused admission to the hospital because of their condition or because they were likely to be "poor risks." The patients in this series were consecutive and included all who were admitted to the public wards during a five year period.

The low operative mortality rate is said to have been due to several factors: (1) proper preoperative care, including drainage by catheter for decreased renal function; (2) appropriate preoperative treatment of cardiac and other medical complications; (3) avoidance of suprapubic cystotomy except when absolutely necessary (this operation being done in only 5 per cent of the cases); (4) treatment by transurethral resection methods when the prostate gland consisted of small lateral or median

45. Vest, S. A.: Mortality in Surgery of the Prostate, *J. Urol.* 45:439-450 (March) 1941.

bars, and (5) performance of prostatectomy when the gland was of moderate or large size.

Perineal prostatectomy is a safe and surgically sound method of treating moderately and extensively hypertrophied prostate glands. It gives excellent functional results, and there is less possibility of recurrence of the obstruction than there is after resection. In addition to the important fact that carcinoma can be recognized early and radically treated through the perineum is the fact that the perineal route affords dependent drainage to an infected bladder and lessens the chances for the development of serious infection of the upper part of the urinary tract.

It is only by the application of these principles and the selection of the proper type of operative procedure for each patient that a mortality rate of 1.6 per cent has been achieved in these cases, and in retrospect Vest thinks several of the 6 deaths that occurred probably could have been avoided. He points out that Young's report of 128, and later of 198, consecutive cases in which perineal prostatectomy had been done without a death concerned largely private patients. Commentators on Young's statistics have held that among patients in public wards the mortality rate is always high. Vest's report of a mortality of 1.6 per cent in 365 operations for the relief of prostatic obstruction among patients in public wards (the mortality rate for perineal prostatectomy alone being 1.2 per cent) shows that with proper care a low mortality rate can be obtained for patients in public wards, who usually enter the hospital in poor condition and with many complications.

Kackley⁴⁶ reports a total mortality rate of 2.4 per cent in a series of 290 cases in which prostatic obstruction was treated by transurethral resection with the galvanic cautery. Delayed hemorrhage was a factor in only 0.6 per cent of the cases. Immediate serious hemorrhage requiring cystotomy occurred twice (with 1 death).

An average of 18.5 Gm. of tissue was removed in each case. Eighty-eight per cent of the patients were free of residual urine within eight weeks, and 90 per cent were free within three months. Particular attention to thorough grooving of the lateral lobes of the gland and to leaving an adequate blood supply to all prostatic tissues is urged.

Davis and Nesbit⁴⁷ present comparative tabulated follow-up data on patients who underwent perineal prostatectomy and prostatic resection for benign prostatic hypertrophy. These data are based on an analysis of replies to questionnaires received at least a year after operation from

46. Kackley, E.: Galvanic Cautery Transurethral Resection: A Report of Two Hundred and Ninety Cases, *J. Urol.* **45**:451-466 (March) 1941.

47. Davis, E., and Nesbit, R. M.: Comparison of Late Functional Results in Perineal Prostatectomy and Transurethral Prostatic Resection, *Tr. Am. A. Genito-Urin. Surgeons* **33**:251-255, 1940.

100 consecutive patients who had been operated on by the one method and 100 who had been operated on by the other.

Although it is agreed by urologic surgeons that both prostatectomy and prostatic resection are major surgical procedures, the ordinary patient who is to undergo prostatectomy, influenced by his visible external incision, is inclined to view his operation more seriously than the patient who undergoes prostatic resection and will therefore more likely choose to remain in the hospital longer than is necessary. The average time required for the cessation of perineal urinary drainage after prostatectomy might serve as a fairer basis for comparison than the average period of postoperative hospitalization. The time required for closure of wounds averaged sixteen and a half days; the time of postoperative hospitalization averaged twenty-one days.

The hazard of postoperative urinary incontinence is to be reckoned with after removal of prostatic obstruction by any of the three recognized methods. Those with experience know that careful and honest analysis of any large series of cases of suprapubic prostatectomy will show that in a small percentage of the cases the operation was defective in this respect. Although no one denies the danger of damage to the external sphincter inherent in perineal prostatectomy, the occurrence of this complication after suprapubic prostatectomy indicates that unsatisfactory urinary control may occasionally result from weakness of the fibers of the external sphincter peculiar to the individual patient or that, possibly, it may result from a concomitant lesion of the central nervous system. Since this particular small follow-up series, consisting of only 100 cases in which replies were obtained, happens to include 2 cases in which real urinary incontinence was present (complete in 1 and partial in 1), the percentage of incontinence following perineal prostatectomy is more apparent than genuine.

Concerning prostatic surgical procedures, it may be said that in general cure may best be gaged by the postoperative frequency of urination by day and by night and, more particularly, by the patient's own satisfaction or disappointment with the degree of symptomatic relief obtained. Eighty-five per cent of these old men stated that they did not pass urine too frequently; 60 per cent reported that they urinated only once or not at all during the night, and 89 per cent voluntarily classified themselves as well.

Modern transurethral prostatectomy has been evolved during the past decade.

Low morbidity and mortality rates and excellent postoperative results can be obtained after resection if four cardinal principles are rigidly observed. They are: (1) avoidance of infection; (2) adequate control of hemorrhage during operation; (3) prevention of injury of the urethra, and (4) subtotal removal of the prostate gland.

The careful management of patients before, during and after operation by means of aseptic drainage systems has reduced sepsis to the status of an unusual complication.

A well planned and executed routine technic of operation enables the surgeon to control bleeding during operation in a completely efficient manner. The 100 cases of resection reported by Davis and Nesbit include only 1 in which postoperative hemostasis was required.

Subtotal removal of the prostate gland is essential to an uncomplicated postoperative course as well as to a satisfactory end result. It is felt that these can be attained most efficiently by the use of digital palpation during operation. Adequately performed transurethral resection should leave the capsule exposed throughout the prostatic fossa, and the urologist should employ resection only in those cases in which this type of removal can be attained. In other cases the patients should be treated by enucleation. In this series it was necessary to do secondary resection in 6 cases to complete the removal of tissue.

Four patients in this series had previously undergone resection, with imperfect results; Nesbit had operated on 3 of them. In each case an incomplete but seemingly satisfactory amount of tissue had been removed. All the glands were grade 3 in size, and 35, 60 and 52 Gm. of tissue had been removed, respectively, at the first operation. The patients were never entirely free from symptoms until after their return one, five, two and four years later, respectively. Secondary operation with complete removal of tissue yielded 69, 57 and 62 Gm. from 3 patients and had, at the time at which Davis and Nesbit wrote, apparently cured each patient. The fourth patient, a physician, had undergone resection three times previously in another clinic. Completion of prostatectomy for him required removal of 66 Gm. of tissue and resulted in normal urinary function.

It is the practice of Davis and Nesbit to perform open prostatectomy in those cases in which the prostate gland appears to be too large to resect in one operation of an hour's duration.

PENIS

Epithelioma.—In discussing epithelioma of the penis, Naegeli⁴⁸ states that all writers on the subject agree that balanitis or balanoposthitis is the most important single cause of carcinoma of the penis. All writers are in agreement that circumcision of all male infants is the one prophylactic measure of any value. Naegeli reports that Wolbarst reviewed the literature and circularized a number of large hospitals and cancer services. He was unable to find a single instance of the lesion in a Jew circumcised at birth, although he found one in an uncircumcised adult Jew.

48. Naegeli, F. D.: Epithelioma of the Penis, J. Urol. 45:202-215 (Feb.) 1941.

Two types of squamous carcinoma of the penis usually are described, the papillary and the infiltrating type. Neoplasm of either type may arise from the mucous membrane of the glans penis or the prepuce; rarely does it spring from the skin of the shaft behind the corona or from the mucosa of the urethra. Most commonly, the neoplasm is papillary in type and originates on the glans. It starts typically as a small papillary or indurated nodule under a phimotic prepuce and enlarges at a rate proportional to the degree of its malignancy. Soon infection supervenes and a foul, sometimes bloody, discharge oozes from beneath the prepuce, which eventually may be perforated. Infiltration of the glans may result in obstruction to urination or to the formation of fistulas.

Metastasis probably takes place by embolism or by migration of a group of malignant cells whose travels terminate in the first lymph node encountered. Early removal of the primary lesion prevents embolic dissemination. The majority of patients suffering from carcinoma of the penis have palpably enlarged inguinal lymph nodes when they are first examined, but somewhat less than half of these nodes contain carcinoma cells. The enlargement in the rest is due to infection in the region drained by the tributary lymphatic vessels. Since it is frequently impossible to distinguish by palpation which glands are affected by metastasis, it may be desirable to defer dissection of the glands for a time after removal of the primary tumor to allow the adenitis to subside. Such a procedure may reduce the mortality rate of the combined one stage operation, particularly among patients whose general physical condition is poor.

There is no uniform sequence of the appearance of symptoms. Commonly, symptoms are not present until the primary lesion is extensive and metastasis is present. Drainage, or an increase in drainage, from beneath a phimotic prepuce may attract attention. Bleeding occurs in 10 to 20 per cent of the cases. Obstruction to urination and the formation of urinary fistulas are late developments. Enlargement of portions of the groins may occur at any time during the course of the disease, even before the primary lesion is noticed. The time elapsing between the appearance of the first symptoms and the visit of the patient for treatment in most instances averages from ten months to two and a half years.

All the forms of therapy for cancer have been applied to carcinoma of the penis, including the surgical, the electrosurgical, the radiotherapeutic and combinations of these.

Electrocoagulation of the primary lesion and electrodissection offer no advantages over surgical treatment. Fulguration frequently does not remove all the cancerous tissue, and it has been said that some tumors

are stimulated to more rapid growth after its use. Moreover, the penile scars which follow treatment by fulguration frequently are deforming and painful.

Radium is useful in carefully selected cases.

High voltage roentgen therapy has proved disappointingly ineffective against both primary and metastatic epithelioma of the penis, even when administered in fractional doses by the Coutard method.

The lesion rarely recurs in the penile stump, but it does recur in the groins. Evidence of its existence in the latter site usually appears within two years, although the literature directs attention to not a few instances in which it recurred four or five years after inguinal dissection. Occasionally, cure has resulted from secondary removal of the involved region. Roentgen and radium therapy have proved unsatisfactory for the control of recurrence.

Records of the 26 patients considered by Naegeli contain some mention of the presence or absence of phimosis. Phimosis was present in 20 instances; in 18 of these it was probably congenital. Six patients had been circumcised prior to admission; 4 from three months to three years after symptoms of cancer had developed; 1 twenty months, and 1 fourteen years, before cancer was noted.

URETHRA

Plastic Procedures.—In regard to extensive stricture of the urethra Dodson⁴⁹ states that it is well recognized that if a strip of mucosa can be preserved a satisfactory urethral channel will form about an indwelling catheter, provided healthy perineal tissue to be approximated over the catheter is present. When this treatment is not possible, most authors advise performance of perineal urethrostomy to create a permanent stoma.

When the perineal tissue overlying and supporting the urethra is injured or destroyed, the problem of successful repair of a urethral defect is much more difficult. Confronted with 2 patients who had such a condition, Dodson considered that the scrotum was the logical source from which to obtain tissue to aid in reconstruction of the urethral channel and to give the channel support and protection. The posterior portion of the scrotum can easily be shifted to the perineum. It has an abundant blood supply, which need not be interrupted, and the texture of the scrotal skin is but slightly different from that of the perineum.

In Dodson's first case a portion of the bulbous urethra was resected because of carcinoma. The local neoplasm was extensive and required excision of all neighboring perineal tissue except a portion of the skin.

⁴⁹ Dodson, A. I.: Transplants from the Scrotum for the Repair of Urethral Defects, *Tr. Am. A. Genito-Urin. Surgeons* 33:211-220, 1940.

The subcutaneous tissue of the scrotum was used to help bridge the gap in the urethra, to create an additional blood supply for the region and to furnish subcutaneous support.

The perineal urethra of Dodson's second patient was partly destroyed, and the overlying perineal tissue, including the skin, was entirely destroyed by periurethral phlegmon. A whole thickness graft from the scrotum was used for repair of the defect.

Davis⁵⁰ states that the Thiersch-Duplay method continues to be the foundation stone of the operative structure in the surgical treatment of hypospadias in men. It results in a hairless urethra of uniform caliber, and there is no limit to the length of the urethra which can be constructed. It is, however, difficult to carry a urethra that has been formed by the Thiersch-Duplay method fully to the end of the penis. For this reason and in view of the recent increased interest among plastic surgeons in pedicled tube grafts, Davis turned again to this oft-tried procedure.

A rectangular flap of skin is outlined on the dorsum of the penis. The pedicle is produced at the proximal end of this flap, and at this end its edges are made to diverge so that the new meatus will be sufficiently large and any tendency to contracture will be avoided. The sutures used are interrupted and are of the finest plain catgut (at first no. 000; later, no. 0000).

With this arrangement it was soon found that the blood supply was much better than it was when the flap was left attached by its distal end. Consequently, the tube graft could be made as long as the length of the penile skin allowed, without sloughing. The proximal attachment also allowed the penis to be bent over dorsally, so that the entire length of the tube graft could be utilized. The procedure finally evolved was to measure the length of the tube graft and then to measure an equal distance on the central surface of the penis, beginning at the tip of the glans. Over this distance a tunnel was produced by means of a sharp-pointed bistoury, and it was enlarged by means of a grooved director and scalpel to such a size that the tube graft could easily be drawn through it. The tube graft was fastened in place by four sutures which joined its extremity to the adjacent skin, and by three sutures at the new meatus, all of no. 000 plain catgut. In some cases, a single additional suture of fine black silk was placed at the meatus.

The results of this procedure show that the grafts survived perfectly in all of 6 cases.

After the lapse of two or three weeks, the pedicle is divided, so that the meatus is left situated at the tip of the glans in its normal and proper position.

50. Davis, D. M.: The Pedicle Tube Graft in the Surgical Treatment of Hypospadias in the Male and a New Method of Closing Small Urethral Fistulae. *Tr. Am. A. Genito-Urin. Surgeons* 33:221-235, 1940.

The new glandular urethra may be joined to the original urethra by a Thiersch-Duplay plastic procedure during the same operation, or if there is any reason for delay, the joining may be done later. The covering-in phase of the Thiersch-Duplay plastic procedure, to complete the new urethra, has always been a difficult part of the technic. If penile skin is used, it must be brought together under considerable tension, and in addition the suture line in the skin lies directly or almost directly over the suture line in the new urethra, so that the development of persistent fistulas is practically inevitable. This may be avoided if the anterior surface of the scrotum is incised and the penis is sutured down to the scrotum.

The small fistulas which frequently remain after construction of a new urethra constitute perhaps the most annoying and discouraging feature of surgical operation for hypospadias. The method Dodson has evolved for closing them has succeeded on every 1 of 4 consecutive occasions, an impressive record. After the fistula is cut around and the skin is undermined in the usual way, a straight needle threaded with silk thread is inserted eye first in the new meatus and is brought out through the fistula. The cut outer edges of the fistula are caught with the silk thread, and the other end of the thread is passed out again through the meatus. The result is that when the two ends of the thread are pulled the fistula is turned completely inside out and made to project into the lumen of the urethra. This inversion of the fistula is maintained by fastening the thread to the abdominal skin through an intermediary rubber band. The silk thread pulls out within from two to four days, but by this time healing is almost complete.

The methods described by Davis have been used for 6 other patients who were in various stages of treatment at the time of his report. These methods have been beneficial and lend a new note of confidence to operative plans and procedures. Davis adds a note of warning, however, stating that the surgical treatment of hypospadias is a fascinating procedure for those willing to devote the time and effort necessary to become competent in it but that it should not be attempted by any others, since neither the surgeon nor the patient is likely to benefit from inexperience or lack of careful attention and application to the exacting technic required.

Nesbit⁵¹ states that operations for the correction of hypospadias in men are designed to fulfil two purposes: (1) correction of ventral deformity and (2) construction of a penile urethra.

The ideal attainment of these two objectives should provide an end result in which the phallus is free from ventral scar, so that normal

51. Nesbit, R. M.: Plastic Procedure for Correction of Hypospadias, *Tr. Am. A. Genito-Urin. Surgeons* 33:237-239, 1940.

sexual function is possible, and in which the urethra is of adequate caliber and is entirely free from growth of hair.

Nesbit believes that the procedure with which his report is concerned allows attainment of these objectives. It provides for correction of deformity at the first stage without any midline scar and leaves the ventral surface covered with normal skin which bears no hair and subcutaneous tissues which are freely movable on the subjacent penile structures and are thus suited for the Thiersch, the Duplay or the McIndoe type of urethroplasty.

Circumcision is carried out 0.5 cm. from the corona. Subcutaneous dissection denudes the phallus easily except at the midline on the ventral surface, where there are situated the fibrous remains of structures embryologically designed to cover the corpus spongiosum. These fibrous elements are completely removed by sharp dissection, so that straightening of the penile shaft with a relatively proximal displacement of the urinary meatus is allowed. A buttonhole incision is now made in the dorsal skin flap at a suitable point, and the glans penis is brought out through it. A line of interrupted silk sutures fixes the free edges of the buttonhole incision to the skin adjacent to the corona. The skin flap distal to the buttonhole incision now folds downward to cover the ventral defect, and final closure is made by a transverse suture line.

Experience with a number of patients who have undergone this first stage procedure has demonstrated its value. Such patients have obtained complete correction of deformity, and the skin graft which has been transplanted from the dorsal to the ventral surface has been devoid of scar. It moves freely on subjacent structures.

Urethroplasty by means of the technic of Thiersch or of Duplay is performed easily and advantageously at the second stage. The fact that the skin and subcutaneous structures are normal facilitates the handling of them, and the increased circumference of the penile integument which results from the first stage procedure helps materially to prevent the exertion of any tension on suture lines on closure of the outer edges of the skin. Further, the urethra is lined by skin which is not hair bearing.

Nesbit prefers the Duplay type of urethroplasty, in which stainless steel subcuticular sutures are utilized for closure. With this technic, only two sutures are needed for the entire urethroplasty: one for closure of the urethral skin tube; the other for closure of the outside skin wound. These stainless steel sutures cause a minimum of reaction and infection and are easily removed on the fourteenth postoperative day.

Diverticulum.—Parmenter⁵² discusses diverticulum of the urethra in women and reports 8 additional cases.

52. Parmenter, F. J.: Diverticulum of the Female Urethra, *J. Urol.* 45:479-486, (March) 1941.

There is no general agreement on the question whether the origin of the diverticulum is congenital or acquired. Probably both views are correct.

A diverticulum of the urethra may cause frequency, urgency and difficulty of micturition, a lump in the vagina, pain on walking or during coitus, or an intermittent discharge from the urethra.

The diverticulum, which feels soft and fluctuating, can be easily recognized on vaginal palpation. If pressure is exerted on it with the labia separated, pus, urine or both will be seen to drip from the meatus with disappearance of the mass. Cystourethroscopy will demonstrate one or more openings, usually situated on the floor of the urethra or slightly above on the lateral walls. The opening of the diverticulum usually is situated just in front of the sphincter muscle. A small ureteral catheter can be passed and will coil up in the diverticulum and be readily shown in a roentgenogram. The important point in diagnosis is careful palpation of the urethra through the vagina. The diverticulum, even if small, can be easily identified. It is necessary to separate the labia so that the expressed secretion may be seen as it leaves the meatus.

Successful treatment may be conservative or radical, although the latter undoubtedly is the method of choice except under exceptional circumstances. The technic used is radical removal of the sac, which is ligated and amputated at the urethral junction. The stump is inverted up into the urethra by two layers of interrupted no. 00 chromic gut sutures. The mucous membrane is closed with no. 1 chromic gut suture. Silk is not used, because it may play the part of a foreign body, as it did in one of Parmenter's cases of vesicovaginal fistula. An indwelling catheter, which must be kept draining, is left in place for ten days. The vagina is also lightly packed with gauze soaked in an approved antiseptic agent, and the gauze should be changed either daily or every other day, as indicated. Use of one of the ordinary urinary antiseptic agents, which has been utilized internally a few days prior to operation, is continued.

Engel⁵³ calls attention to urethral diverticulum in women, a lesion which he believes is commonly overlooked.

The bulk of evidence favors the theory of acquired origin of this condition, and he believes that the lesion arises from infected periurethral glands which, in reality, form periurethral cysts which later rupture into the urethra.

There are no characteristic symptoms, but a urethral diverticulum should be suspected in any patient with a history of swelling in the anterior wall of the vagina or about the urethra. Any woman with recurrent or persistent vesical symptoms should be asked about this item when the history is being obtained.

53. Engel, W. J.: Diverticulum of the Female Urethra, *J. Urol.* 45:703-709 (May) 1941.

The treatment of choice is surgical removal; it was carried out in 4 of Engel's 5 cases with completely satisfactory results.

TESTIS

Tumor.—Huffman⁵⁴ reports a case of unusual testicular tumor which presumably originated from the interstitial cells, and discusses the subject of interstitial cell testicular tumor. Including Huffman's case, there have been reported 13 cases of tumor of this type. In 6 cases the tumor was on the left side; in 5 it was on the right; in 1 it was bilateral, and the side affected in 1 case is not known. In 5 of these cases the condition appeared in childhood, and in 4 of these precocious puberty occurred. In 2 of these 4 cases regression of the secondary sexual changes occurred after orchidectomy. Huffman's case is the only instance in which the condition of gynecomastia occurred during the childhood of the patient. In 2 adult persons gynecomastia occurred, but regression ensued after orchidectomy.

Ormond and Prince⁵⁵ review cases of malignant tumor of the testis in which the patients were seen at the Henry Ford Hospital, Detroit, during the twenty-six years prior to their report; they discuss some points of special interest.

The most common symptoms are swelling and pain, but swelling is observed twice as often as pain. Other symptoms reported are abdominal tumor and loss of weight.

During the quiescent period of growth, the neoplasm is limited by the resistance of the tunica albuginea testis and for a long time retains the shape of an enlarged testis. The shape is typically oval, although spherical tumors are sometimes encountered. The consistency varies greatly. The smaller, slowly growing teratomas may be of uniform stony hardness, but the larger tumors, which contain portions of cartilage, cystic portions and portions of soft vascular carcinoma are of course irregular. Almost all tumors in the series reviewed by Ormond and Prince were smooth, and none were large.

Hydrocele is said to accompany testicular tumor in from 15 to 25 per cent of the cases, and it may be necessary to aspirate the fluid from the hydrocele before the testis can be palpated accurately.

Metastasis from tumor of the testis occurs chiefly by way of the normal lymphatic drainage of the testis, that is, along the spermatic artery to the retroperitoneal lymph nodes. Then the spermatic, epigastric, mediastinal and supraclavicular glands may become affected.

54. Huffman, L. J.: Interstitial Cell Tumor of the Testicle: Report of a Case. *J. Urol.* **45**:692-698 (May) 1941.

55. Ormond, J. K., and Prince, C. L.: Malignant Tumors of the Testicle. *J. Urol.* **45**:685-691 (May) 1941.

Trauma has often been credited with inciting the growth of tumor in the testis, but it seems rather well agreed now that one physical insult could hardly cause malignant degeneration, especially in view of the fact that the trauma to which it is attributed is often of a relatively unimportant nature and in view of the vast number of similar instances of trauma which are not followed by the formation of tumor. Trauma to the testes is common, and it is easy to attribute increase in the size of a tumor to a previous episode of trauma. However, it is possible that trauma may excite rapid growth in a small preexisting tumor or that it may serve to call attention to a neoplasm hitherto unnoticed. The series of Ormond and Prince is somewhat unusual in that trauma was mentioned as a possible cause of the lesion in only 4 instances.

The relation of cryptorchidism to tumor has aroused much discussion. The question is not yet settled, but it seems probable that cryptorchidism is a factor of importance, and this probably constitutes an added reason for the performance of orchidopexy. Of the 21 patients included in this report, 1 was a cryptorchid.

There are two chief forms of tumor which affect the testis: the homogeneous tumor, composed of cells of a single type, and the mixed tumor, or teratoma.

There are at present five methods of treatment: (1) orchidectomy alone; (2) roentgen therapy alone; (3) orchidectomy followed by roentgen therapy; (4) orchidectomy with preoperative and postoperative roentgen therapy, and (5) radical orchidectomy with removal of the draining lymphatic vessels.

Orchidectomy alone is now rarely practiced, and in most series of such cases in the literature dismal results are reported. However, Rees treated 38 patients by orchidectomy alone and obtained a four year survival rate of 13.2 per cent.

The method advocated by most urologic surgeons is orchidectomy followed or both preceded and followed by roentgen therapy, and these two modifications of the operation seem to have about an equal number of adherents. Ormond and Prince report that Dean and Barringer of the Memorial Hospital for the Treatment of Cancer and Allied Diseases, New York, are the chief proponents of both preoperative and postoperative roentgen therapy and that their results are extremely good. Whether the results would have been any worse if the preoperative treatment had been omitted may be questioned.

The Mayo Clinic reported long survival obtained by repeated courses of roentgen treatment in patients who had massive metastasis.

The radical operation is used by few. The mortality rate for this operation is high. Moreover, considered theoretically, on the basis of the anatomy of the lymph vessels, the radical operation seems to be

contraindicated, for the drainage from the testes frequently is to the lymphatic vessels on both sides of the aorta, and crossed metastasis has been observed.

Of those patients in whom metastasis was not demonstrable at the time of operation, only 2 were known to be dead at the time Ormond and Prince made their report; 5 patients, or 50 per cent, lived for more than five years; 7 patients, or 70 per cent, lived for more than four years. Moreover, the ones who received roentgen therapy were living, and the 2 who died had received none.

Of those patients in whom metastasis was demonstrable at the time of operation, all who had been traced were dead, except 1 who had lived five months after operation at the time of the report. None lived more than two years, and most died within a year. In view of the results obtained by others, this would indicate that the patients with metastasis probably received an inadequate amount of roentgen treatment.

Two conclusions seem to be inescapable: (1) that the presence or absence of demonstrable metastasis is of great prognostic significance and (2) that adequate roentgen therapy is of great importance.

Barringer and Earl⁵⁶ report the results of a survey of 37 cases of teratoma testis in which necropsy was done. The ages of the patients ranged from birth (1 stillborn child) to 47 years.

Records such as these have clarified many points as to the path of metastasis and the reasons for the inadequacy of radiation therapy for many of these patients. Metastasis may be, and generally is, both lymph borne and blood borne. If a left supraclavicular signal node is present, there is probably a chain of nodes with metastatic involvement along the course of the thoracic duct.

The lungs were involved in 78 per cent of the cases. The liver was involved in 75 per cent of the cases in which there was pulmonary involvement. The genitourinary tract was involved in 24 per cent of all the cases. The mediastinal nodes were involved in 55 per cent of the cases in which there was pulmonary metastasis. In 72 per cent of all the cases there was bilateral involvement of the abdomen, either of the lymphatic glands or of the intra-abdominal organs, such as the liver, the kidneys or the spleen.

Randall and Chamberlain,⁵⁷ in discussing the results of the treatment of testicular tumors for which preoperative roentgen therapy was carried out, state that they observed 17 patients for whom the prognosis was hopeless because of metastasis. Many died soon after the beginning

56. Barringer, B. S., and Earl, D.: Survey of Thirty-Seven Autopsied Cases of Teratoma Testis, *Tr. Am. A. Genito-Urin. Surgeons* **33**:269-295, 1940.

57. Randall, A., and Chamberlain, G. W.: Results of Treatment of Testicular Tumors: Analysis of the Advantage of Pre-Operative Roentgen Therapy, *Tr. Am. A. Genito-Urin. Surgeons* **33**:297-299, 1940.

or during the course of irradiation of their tumors. None of those with metastasis that extended above the diaphragm lived. Judged in the light of recent observations, only 8 of the 17 patients received adequate treatment. Of these 8, 3 were still living and well at the time of the report, three, eight and a half and eleven years, respectively, after removal of the primary tumor. These cases and many others reported in the literature conclusively demonstrate the value of radiation therapy in the treatment of a malignant growth of the testicle. Opinions differ, however, as to when such therapy should be instituted.

In 1932 Randall and Pancoast advocated and began the preoperative irradiation of tumor of the testis. The distal portions were treated first, and the testicular tumor was irradiated only after treatment had been administered to the lymphatic vessels draining the testes. The blood counts were watched, and the tumor was removed four to six weeks after treatment. Twelve patients were treated by this method. Eleven were living and well at the time of the report.

Ninety-one per cent of the 45 patients whose tumors were irradiated before operation were living and well two or more years after treatment. Fifty-six per cent of those who had been operated on and had then received radiation therapy before there was clinical evidence of metastasis were living and well two or more years after treatment, and 17 per cent of those who received delayed radiation treatment were living at the time of the report.

On the basis of this study, Randall and Chamberlain recommend the following procedures for the treatment of malignant tumor of the testis: (1) prompt diagnosis by means of the history, the results of physical examination and the results of studies of the urine for gonadotropic content of excretory urograms for the detection of abdominal tumors, as well as of roentgenograms of the involved testis and the thorax; (2) preoperative irradiation of the region of primary and secondary lymphatic drainage of the testis, and then of the tumor itself, and (3) orchidectomy within approximately four weeks.

Cahill⁵⁸ discusses testicular tumor and reports on the radical operation for this condition. This operation for tumor of the testis seems to occupy an uncertain position among urologic procedures. The concentration of tumor therapy as a whole in the hands of those who employ radiation and the radiosensitivity of certain of the testicular tumors have resulted in the presentation of well tabulated studies on such tumors and the effect of radiation on them, with or without castration.

The radical operation seems to have had the benefits of no such studies. Hinman, however, reported on the frequency of performance of the operation. Thirty-five surgeons reported to him by letter that

⁵⁸ Cahill, G. F.: Testicular Tumors: A Report upon the Radical Operation. *Tr. Am. A. Genito-Urin. Surgeons* **33**:301-309, 1940.

they had done the operation in 91 cases. To these 91 cases he added 9 of his own, bringing the total to 100 cases in which the operation had been performed. Up to the time of Cahill's report, a relatively small number of urologic surgeons had given the procedure more than a casual trial. Ten surgeons had done 63 of the 100 operations. Of particular interest in Cahill's report is the fact that 20 patients, or a fifth of all the patients operated on, had lymphatic metastases impossible to remove, so that the planned procedure could not be carried out. The attempts at surgical removal of widespread metastases of tumors situated elsewhere have not been productive of good results, so that no better results may be expected from such removal of metastases of testicular tumors.

After several attempts to remove metastases which could not be separated from essential vessels, a study was made of those cases in which the patients afterward were submitted to the radical procedure, to ascertain, if possible, whether or not metastases were demonstrable. A supraclavicular metastasis is palpable; an intrathoracic metastasis can be shown by roentgenograms if it is in the pulmonary tissues; it is also demonstrable if it is in the mediastinum. An extensive epigastric or retroperitoneal metastasis is palpable. The usual metastatic pathway from the testis is in the same fascial planes as the ureter and crosses the same lymphatic vessels. It may and does involve the lymphatic vessels near the hilus of the kidney and the edge of the psoas muscle or the preaortic group. Some of these planes and tissues may be outlined roentgenographically. Cahill endeavored to determine by roentgen examination whether there were changes in the edges of the psoas muscles or in muscle shadows and by intravenous urography and retrograde pyelography whether there were extrinsic apparent deflections of the ureter or the pelvis. In cases in which the metastatic involvement is extensive, such changes are marked. This was shown in 2 cases; in both there was extensive involvement by a tumor secondary to the one in the testis. Involvement of the kidney or the ureter itself may occur, as was demonstrated in a case in which a metastatic mass secondary to a testicular tumor involved the ureteropelvic junction, causing hydronephrosis. When such obvious extension is present, radical surgical treatment is not feasible.

Cahill cites 55 cases of testicular tumor recorded in the J. Bentley Squier Urological Clinic, New York. Those in which the patients were treated directly by the radiotherapy department were not included. Eighteen patients were selected for radical operation. For 17 of these primary complete operations had been attempted, and for 1 a secondary radical operation had been tried. In 3 of the operations done between 1928 and 1932 irremovable metastatic processes had been encountered. In this same period the 1 secondary radical operation (removal) just mentioned had been attempted. Since 1932 all the patients selected for

the operation were patients concerning whom no criteria could be developed that would show extension of the tumor previous to operation. In all these patients the operation was completed primarily. In 5 of the 14 cases in which the operations were completed, tumor cells were demonstrated microscopically somewhere in the lymph nodes or vessels in the removed tissue.

Three patients who had been operated on before 1932 died of the disease; in all these the operation had been incomplete because of metastasis which should have been demonstrated previously. All had tumor masses which involved the preaortic vessels. With subsequent experience these patients would not have been selected for the procedure.

When this particular operation was considered in the light of those cases in which it was completed, Cahill found himself in accord with Hinman as to its feasibility and as to the ease of dissection of the primary preaortic lymph zone from the testis. There were no complications or operative deaths in Cahill's 18 cases. The healing of the larger incisions was uniformly rapid, and there was at the time of writing no weakness or hernia in any of the cicatrices.

A comparison of the results obtained by this operation with the results obtained in the 37 cases in which irradiation of the tumor was practiced with or without castration showed, at the time of the report, 17 of the 37 patients dead of the disease in contrast with 3 of the 18 patients for whom radical operations had been attempted or completed.

Randall,⁵⁹ in discussing the treatment of patients with testicular tumor, states that it is a rare privilege to be able to look back over the short period of ten years and see a definite radical change in the whole procedure of helping these patients to become well again. He calls attention to Tanner's report dealing with 425 cases of orchidectomy alone; the results presented four years after operation showed that only 5.3 per cent of the patients were cured. If Tanner had said that the mortality rate was 94.7 per cent, Randall says, he would thereby have emphasized the acute need of a change in the therapeutic program for such patients. Tanner's report was followed by that of Wasterlain, who recorded a "cure" rate of 6 per cent, so that again a mortality rate of approximately 94 per cent obtained.

It was then that Hinman brought out his radical operation. In his first report it was seen that the average rate of cure had increased to 17 per cent or, conversely, that the rate of failure had receded to 83 per cent.

Hinman concluded his remarks with a succinct sentence: "Orchidectomy, even with early diagnosis, is a dismal failure." This was aug-

⁵⁹ Randall, A., in discussion on papers of Barringer and Earl,⁵⁶ Randall and Chamberlain⁵⁷ and Cahill,⁵⁸ *Tr. Am. A. Genito-Urin. Surgeons* **33**:310-314, 1940.

mented later by a remark Keyes made, namely that in the treatment of tumors of the testis "without irradiation prognosis is utterly bad." For twelve years Randall and Chamberlain have been attempting to change this picture. Their material has not been nearly so great as that indicated by the figures which come from the Memorial Hospital and from Hinman's clinic, but they are happy to be able to report a cure rate of 91 per cent and a mortality rate of only 9 per cent. Thus, within ten years there has been a complete reversal of the picture in the matter of this particular disease.

A number of urologists emphasize one criticism of preoperative irradiation of the tumor, that by this means lesions are destroyed, so that the histologist is not able to state definitely the type of tumor which has been destroyed. This may be said to be the pathologic point of view. Consideration of the patient should and does come first. Randall and Chamberlain know of 1 interesting case in which because of an error in the technic of irradiation a gap of about 1 cm. occurred between the lead screen and the limit of the application of the roentgen rays over the region of the right groin. This case was interesting in that it was proved by surgical removal that the tumor was situated in precisely the portion of the tissue affected by the gap in the screen.

Chamberlain presents (and Cahill has had similar experiences) 3 or 4 cases in which abdominal metastasis pushed the kidney out of place, rendering it nonfunctioning (by displacement or pressure on blood vessels or ureteral occlusion) but in which the kidney regained normal function (bilaterally) after radiation removed the abdominal metastatic process. Such cases, first, constitute evidence of what renal function can and will do, and, second, impressively show the effect of radiation on such metastatic neoplasms.

Other considerations that should be accentuated are, first, essential irradiation of the supraclavicular region and the starting of irradiation from the periphery toward the primary tumor, and, second, deferment of diagnostic study of such a patient until a urogram has been made according to the intravenous technic.

Barringer,⁶⁰ in discussing testicular tumors, congratulates Chamberlain on his excellent results in the matter of recovery, a rate of 91 per cent in cases in which the opportunities were most favorable. He commends Cahill for his extraordinary percentage of operative cures. He was inclined to believe that such figures as Randall and Chamberlain presented will be lessened as more cases are recorded.

Barringer mentions irradiation of one testis and the possibility of inflicting damage on the other by this procedure. This is a most

60. Barringer, B. S., in discussion on papers of Barringer and Earl.⁵⁹ Randall and Chamberlain⁵⁷ and Cahill,⁵⁸ *Tr. Am. A. Genito-Urin. Surgeons* **33**:310-314. 1940.

important point in the minds of all patients. He thinks that some damage is inflicted on the other testis (the uninvolved one) no matter how carefully it is screened. Lead screens may be placed around it, but no matter what is done, it receives radiation to some extent. The spermatogenic function as evidenced by the presence of viable spermatozoa disappears within six months. In some cases this function may reappear about two and a half years later.

Barringer draws attention also to 5 of Cahill's cases. In all cases the tumor was seminoma, which is notably radiosensitive. Barringer says that he would rather undergo irradiation of such a tumor than the operation. Yet he thinks it questionable that radiation will control a radiosensitive tumor with small metastases.

UROGRAPHY

Smith and Leadbetter,⁶¹ in discussing intravenous urography, state that the data obtained from a series of persons with severely damaged kidneys were analyzed in an attempt to learn which tests of renal function will reveal whether intravenous urography may be expected to give satisfactory results. They found 2 instances in which satisfactory pyelograms had been made of kidneys that were unable to concentrate to a specific gravity of more than 1.008 or 1.009. Adequate excretion of the medium may be obtained when the concentration of nonprotein nitrogen in the blood is as high as 50 mg. per hundred cubic centimeters.

The most constant indication of the inability of the kidneys to excrete urographic mediums in concentrations sufficient to cast a shadow has been a low excretion of phthalein. Kidneys with a phthalein output which is less than one third normal are unlikely to give satisfactory results with intravenous urography.

Bourne and Hefke⁶² state that the intravenous technic of urography for infants and young children has not been altogether satisfactory. In many instances shadows cast by intestinal gas obscure the urogram to the point of unreadability.

Even careful preparation by the administration of laxative agents, enemas and pitressin does not improve the diagnostic results in pyelography for such patients. Much of the gas in the intestinal tract is caused by air which is swallowed when the child cries and sobs during the procedure.

According to Bourne and Hefke, tomography offers a new method for improvement of intravenous pyelography for infants and young children. This procedure allows the reproduction of certain layers of the body, with elimination of shadows of other layers which may lie

61. Smith, G. G., and Leadbetter, W. F.: A Note on the Limitations of Intravenous Urography, *Tr. Am. A. Genito-Urin. Surgeons* **33**:137-143, 1940.

62. Bourne, N. W., and Hefke, H. W.: Body Section Pyelograms in Children, *J. Urol.* **45**:296-302 (March) 1941.

either above or below the desired level. This is done by blurring the otherwise clearly defined layers. The x-ray tube and the film carrier (Bucky tray) are moved in coordinated opposite directions by a two-armed pendulum which moves with an adjustable axis. The upper arm carries the tube, and the lower arm carries the film tray. At the level of the fulcrum all objects are clearly defined in a layer which is about 1 cm. wide. The method produces a roentgen demonstration of a layer of the body which traverses the renal pelves, calices and ureters. The interfering gas shadows are blurred and do not obscure the pyelographic details. In most cases in which unsatisfactory pyelograms would result from the intravenous technic, good diagnostic roentgenograms can be produced by the simple procedure of tomography.

HYPERTENSION

Nesbit and Ratliff⁶³ state that experimental evidence and clinical observations have shown that hypertension may result from pathologic conditions of the kidney; these may be bilateral or unilateral.

Three different types of unilateral renal lesions are most commonly associated with hypertension: (1) those produced by gross occlusion of the renal arteries, including trauma to the kidney; (2) the obstructive uropathologic conditions, and (3) chronic inflammatory lesions.

Since chronic infection appears to be the most important single causative factor, it seems that the best treatment of this type of hypertension is prophylaxis. In this regard the value of modern chemotherapeutic methods for prevention of chronic infections of the urinary tract cannot be overemphasized.

Nesbit and Ratliff believe that hypertensive patients should be submitted to complete urologic study as a part of the routine examination, even in the absence of a history of renal conditions or of urinary observations suggestive of disease of the urinary tract.

The rational treatment of the hypertensive patient suffering from unilateral nephropathy is removal of the diseased kidney, provided that the function of the opposite kidney is not importantly reduced. If this restriction is borne in mind a reasonable expectancy of improvement or cure can be had in the majority of cases.

Wear and Jacobsen⁶⁴ state that secondary hypertension occurs among approximately a third of the patients with prostatic obstruction. More than 50 per cent will report some evidence of unstabilized blood pressure. Residual urine in the bladder is not the sole factor in the elevation of intrapelvic pressure. Pyelectasis and ureterectasis are the

63. Nesbit, R. M., and Ratliff, R. K.: *Hypertension Associated with Unilateral Renal Disease*, J. A. M. A. **116**:194-199 (Jan. 18) 1941.

64. Wear, J. B., and Jacobsen, R. W.: *Observations on the Incidence and Etiology of Hypertension in Prostatic Obstruction*, Tr. Am. A. Genito-Urin. Surgeons **33**:73-76, 1940.

results of increased pressure within the urinary tract and do not constitute an index of hypertension. Increased intra-abdominal pressure results each time the patient attempts to void. Increased intra-abdominal pressure may elevate blood pressure by acting directly on the abdominal vessels or by increasing intraureteral and intravesicular pressures.

SULFANILAMIDE THERAPY

Deming, Sadusk and Wilson⁶⁵ state that the administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine), whether in an acid or an alkaline medium, may be fraught with serious renal or ureteral complications.

Daily studies of the blood and the urine should be made for the free, the total and the acetylated form of sulfapyridine.

It seems unwise to administer this drug in the presence of obstructive pathologic changes in the urinary system.

The concretions of acetylated sulfapyridine are nonopaque to roentgen rays, but this fact should in no way influence the diagnosis.

There is a likely possibility that such concretions may serve as a nidus for further deposition of urinary salts with the later formation of stones.

Should anuria develop, recanalization of the obstructed ureters with lavage of the renal pelvis should be instituted at once, because anuria has resulted in several deaths, which have been reported in the literature. Recanalization should be attempted in the face of even the most serious complications. Successful results were obtained for 2 seriously ill patients with this procedure.

Sadusk, Waters and Wilson⁶⁶ report 2 cases in which complete anuria occurred during sulfapyridine therapy. In both cases anuria was caused by calculi blocking the urinary tract at the ureterovesical orifices. Treatment by means of cystoscopy was successful. The pathologic changes in the upper portion of the urinary tract of a patient who died of a neurosurgical complication consisted essentially of great tubular and capsular dilatation, marked congestion and vacuolation within the glomerular tufts and acute hemorrhagic pyeloureteritis, which extended into the adjacent renal medullary tissue.

Emmett and Hammer⁶⁷ present a study of the prophylactic use of sulfanilamide for the control of postoperative infection of the urinary

65. Deming, C. L.; Sadusk, J. F., Jr., and Wilson, D. E.: Sulfapyridine Anuria. *Tr. Am. A. Genito-Urin. Surgeons* **33**:127-135, 1940.

66. Sadusk, J. F., Jr.; Waters, L., and Wilson, D.: The Treatment of Anuria Due to Sulfapyridine Calculi, *J. A. M. A.* **115**:1968-1973 (Dec. 7) 1940.

67. Emmett, J. L., and Hammer, H. J.: Prophylactic Use of Sulfanilamide to Control Postoperative Infection of the Urinary Tract, *Proc. Staff Meet., Mayo Clin.* **15**:801-806 (Dec. 18) 1940.

tract. The patients followed were women who had undergone gynecologic operations and who had been treated for postoperative retention of urine either by intermittent catheterization or by the insertion of a retention catheter.

The routine procedure adopted was administration of 200 cc. of an 0.8 per cent solution of sulfanilamide (25 grains, or 1.6 Gm.) subcutaneously on the day of the operation; this was repeated daily until the patient could tolerate tablets taken by mouth. Administration of the drug was then stopped, and the patient received 5 grains (0.3 Gm.) of sulfanilamide three times a day. If catheterization had not become necessary by the end of the fourth postoperative day, the administration of sulfanilamide was discontinued. If catheterization was necessary or if a retention catheter was in place, administration of the drug was continued until the patient left the hospital (which in most cases was on the twelfth or fourteenth day after operation). After the patient had been dismissed from the hospital, the specimen of urine that had been obtained by catheterization was centrifuged and a wet smear prepared with Gram's stain and examined microscopically. In most cases cultures were made.

Emmett and Hammer's report is based on the study of 197 patients. The efficacy of treatment was judged by the amount of pus found by microscopic examination of the wet smear of a centrifuged specimen of urine obtained by catheter.

The results of prophylactic treatment in the 197 cases were as follows: The incidence of infection of the urinary tract was only 18 per cent; there was an incidence of 50 per cent in the control group. Of the group of 197 patients, 115 required the use of a retention catheter. The results of the prophylactic treatment of these patients showed an incidence of infection of the urinary tract of 25 per cent; there was an incidence of 72.5 per cent in the control group.

Hibbs, Day, Jung and Brady⁶⁸ report experience with the use of sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) and sulfapyridine in the treatment of gonorrhea in the male. Both drugs are effective agents in the treatment of gonorrhea. Clinical symptoms of the patients whose course was followed throughout the administration of chemotherapy subsided earlier when sulfapyridine was employed than when sulfathiazole was employed. The percentage of failures was greater when sulfapyridine was used (17.5) than it was when sulfathiazole was the drug employed (5.26). Clinical observations in 378 cases and

68. Hibbs, D. K.; Day, A. A.; Jung, R. W., and Brady, J. M.: Preliminary Report on the Use of Sulfapyridine and Sulfathiazole in Gonorrhea, *J. Urol.* 45: 727-732 (May) 1941.

studies of the blood and the urine in a limited number of cases indicated that sulfathiazole is much less toxic than sulfapyridine. Poor cooperation of patients probably accounts for the large number of cases in which there was a lapse after good results had once been obtained. Lack of symptoms referable to chemotherapy is suggested as the reason for this negligence.

Carroll, Kappel and Lewis⁶⁹ state that sulfathiazole is an effective and safe drug in the treatment of staphylococcic infections of the urinary tract. It is readily absorbed when taken by mouth and is eliminated rapidly, mostly through the kidneys. The amount absorbed when the drug is given by rectum is too small to be therapeutically valuable. The rate of absorption from the spinal fluid as compared with that of absorption from the blood is about 4 to 1. A low concentration of the drug in the blood indicates rapid absorption, and if the patient is not recovering rapidly enough, the dosage may be materially increased. Patients receiving the drug should be seen at least every forty-eight hours, so that the physician may inquire concerning symptoms and observe carefully the skin, scleras and the gross appearance of the voided urine. Cloudy urine, oliguria and decreasing renal function should be recognized as serious warnings of temporary renal damage.

HYPERPLASTIC LESIONS OF THE URINARY TRACT

Stirling and Ash⁷⁰ report 21 cases of hyperplastic lesions of the urinary tract.

Hematuria, dysuria or frequency of urination was found in every instance and was usually severe.

Three of the patients had concomitant cysts and carcinoma of the bladder.

Brunn's follicles or nests are invaginations or extensions of surface epithelium, and their subsequent fate depends on whether the epithelial metaplasia progresses to a squamous or a glandular type.

Follicular cystitis is a nonspecific entity, common in any chronic infection.

Several hyperplastic forms of cystitis may be found in the bladder at the same time.

Stirling and Ash describe for the first time a lesion termed "papillary hyperplasia." It may combine one or more features of the other types and is important, since it may simulate tumor.

69. Carroll, G.; Kappel, L., and Lewis, B.: Sulfathiazole and the Staphylococcus in Urinary Infections, *J. Urol.* 45:770-779 (May) 1941.

70. Stirling, W. C., and Ash, J. E.: A Clinicopathologic Discussion of Hyperplastic Lesions of the Urinary Tract, *South. M. J.* 34:358-364 (April) 1941.

VULVAR FUSION

Taylor ⁷¹ reports 2 cases of labial fusion in which the predominating symptoms were urologic. In the first case acquired fusion of the labia majora occurred in an adult woman; it was probably initiated by mechanical irritation. In the second case congenital fusion of the labia minora afflicted a child 7 years of age who was forced to use the vagina as a urinary reservoir.

Partial congenital fusion is probably not uncommon; it may play a definite part in the production of urinary symptoms. Such an anomaly among children should be looked for as a possible cause of infections and of anomalies of the upper part of the urinary tract as well as of such symptoms as frequency of urination, enuresis and incontinence.

INTRAVENOUS FLUID THERAPY

Murphy ⁷² states that clinical observations teach that some patients who have compensated cardiac lesions tolerate well large quantities of fluid, while others who have cardiac lesions of the same kind respond badly. There is no test that will enable the physician to determine beforehand whether a given patient will respond favorably to fluid therapy. Every patient should be thoroughly examined to determine the presence or absence of organic defect. If such a defect is present, regardless of the state of compensation, fluids should be administered in small volume. These should preferably be isotonic, and, most important of all, they should be administered slowly.

Patients not suffering from heart failure will tolerate fluids given in amounts up to 3,000 cc. per day, even when dehydration is absent.

The danger of the intravenous injection of fluid arises when the fluid is given thus to a patient who has an unrecognized cardiac defect and when large quantities of fluid are administered more rapidly than usual. The volume of fluid, the hypertonicity of the solution and the speed at which injection is carried out are important factors in the precipitation of heart failure.

Although many older persons tolerate the intravenous administration of fluids well, it should be remembered that occasionally some do not.

The main safeguard in the intravenous administration of fluids is a good condition of the cardiovascular system. Sufficient examination of the cardiovascular system may be made without special laboratory aids; nothing more than a careful clinical study at the bedside is required.

A study of the hematocrit determinations, the plasma protein, the venous pressure and the vital capacity is of great importance in deciding

71. Taylor, W. N.: Vulvar Fusion: Two Cases with Urological Aspects. *J. Urol.* 45:710-714 (May) 1941.

72. Murphy, F. D.: The Response of the Cardiovascular System to Intravenous Fluids. *J. Urol.* 45:654-663 (May) 1941.

the kinds and quantities of fluids to be administered and the rate of injection, but it does not help much in discerning the ability of the cardiovascular system to accommodate fluids.

The indiscriminate intravenous administration of fluids should be discouraged, and fluids should be given intravenously only when necessary. The established rules concerning the nature, the amount, the speed and the method of giving fluids should be strictly observed.

CHLOROMA OF THE UROGENITAL ORGANS

Mertz⁷³ states that chloroma is a primary disease of the bone marrow characterized by secondary green tumors which are situated throughout the body and which develop in the presence of a rather constant blood picture, that of a myeloblastic type of leukemia.

Chloroma is of especial interest to the urologist because of the frequency with which it affects the urogenital organs. In a series of 130 children with chloroma, some portion of the urogenital tract was invaded in more than 46 per cent. In 34 per cent of the patients there were chloromatous changes in the kidneys, but in only 2 per cent were there similar deposits in the bladder.

Mertz reports the cases of 2 girls with the acute myelogenous leukemia type of the disease. Chloromatous changes were present in the kidneys and the bladder of each patient, and in the ovary of 1.

Causation of the disease is not known.

No bodily tissue is immune to invasion by chloroma. Some portion of the skeletal system of almost every patient is diseased. Mertz cites Rothschild's review of the literature in which it was found that the bones of the skull had been invaded in 73 per cent of the cases.

In cases of renal chloroma both kidneys are usually diseased. Most often the size and the shape of the kidneys are but little altered; yet in some cases large renal tumors are present. The surface of the kidney may be irregular because of the presence of portions of greenish tumor tissue as large as peas on the surface.

Invasion of the renal parenchyma by chloroma is characterized by diffuse, or foci-like, myeloid metaplasia. The infiltrative lesion predominates and is more marked about the vascular channels. Occasionally, the tubules and the glomeruli seem to be embedded in the neoplastic mass, the glomeruli appearing shrunk. The myeloblastic cells do not as a rule invade the urinary channels of the kidney.

The gross picture of the cut surface of the kidney showing the diffuse infiltration type of chloroma is that of a diffuse green triangle-shaped

73. Mertz, H. O.: Chloroma of the Urinary Organs: Report of Two Patients. Each with Involvement of the Kidneys and Bladder. *Tr. Am. A. Genito-Urin. Surgeons* 33:191-203, 1940.

patch or patches with the base or bases situated near the capsule; in some cases the parenchyma may be invaded by linear infiltrations of the chloromatous tissue.

The pelvic mucous membrane may present slightly elevated gray-green portions of chloromatous tissue. These may occur singly or in groups.

The lesion in the bladder in cases of chloroma may be diffuse infiltration of the wall of the bladder (often widespread), or it may be invasion of the wall of the bladder by foci of tumor tissue.

The diffuse type of invasion occurs most often in cases of chloroma in which myeloblastic tissue is present in the testis. It is not uncommon for a large portion of the testis to be involved.

The cause of the green color is not certainly known. Various explanations based on degeneration of the characteristic cells known to be present in chloroma have been proposed, but none have been generally accepted. Mertz quotes Askanazy's opinion that "the chloromata contain a pigment elaborated by a family of cells originating from the myeloid system." However, this accounts for the green color only in this disease, and the existence of Askanazy's crystals has been questioned.

Chloroma occurs more often among children than among others. Burgess found 23 years to be the average age of all patients, and Foot and Jones state that the average age of young men with the disease is 18.8 years. Seventy per cent of Atkinson's patients were men. The disease runs a rapid course, and death occurs within from a few months to a year and a half.

The clinical course of chloroma is rapidly progressive and ends in death. No method of treatment known at present seems to influence the downward course of the patient in any marked degree. Treatment has been principally supportive.

RETROPERITONEAL TUMORS

Wishard⁷⁴ states that the high incidence of abnormality of the urinary tract caused by retroperitoneal tumors warrants careful urologic investigation in every case in which the condition is suspected. The site and the tissue of origin vary widely.

Retroperitoneal tumors which affect the urinary tract are those involving the autonomic nervous system, angioma, lipoma, sarcoma, post-peritoneal metastasis from primary lesions situated elsewhere and adenopathy incidental to systemic glandular disease.

74. Wishard, W. N., Jr.: Retroperitoneal Tumors and the Urinary Tract. Including Case Report of Spontaneous Perirenal Hemorrhage, *Tr. Am. A. Genit. & Urin. Surgeons* **33**:43-56, 1940.

These tumors may alter the urinary tract by pressure, obstruction, displacement, compression, distortion, invasion, inclusion hemorrhage or sepsis.

Spontaneous perirenal or retroperitoneal hemorrhage is rare. It may be caused by lesions in or outside the kidney. The correct diagnosis of spontaneous perirenal hemorrhage is difficult, and it rests on pain in the renal fossa, syncope caused by concealed hemorrhage and a mass of increasing size. Cystoscopy, pyelography and paracentesis may contribute important diagnostic data but should be used with discretion. The treatment is surgical.

Wishard presents a case in which spontaneous perirenal hemorrhage due to a highly undifferentiated retroperitoneal tumor was demonstrated.

MALE CLIMACTERIC

Douglas⁷⁵ states that there is a transitional phase in the life of the adult man which may be likened to the climacteric of the adult woman. This transition occurs in the middle or late forties. The diagnosis of the climacteric in the adult man is based on urinary disturbances, malfunction of the neck of the bladder, fatigue, indecision, hot flashes, nocturnal diaphoresis, decreased libido, impending impotence and some degree of prostatic involvement.

In those cases in which no abnormality is present, the secretion of gonadal substance may be stimulated by the use of testosterone propionate in doses as small as 30 mg.

The diagnosis and treatment of the transitional phase in adult male life have demonstrated that testosterone propionate is a valuable addition to the urologist's armamentarium.

75. Douglas, R. J.: The Male Climacteric: Its Diagnosis and Treatment, *J. Urol.* 45:404-410 (March) 1941.

Obituaries

DEAN DEWITT LEWIS, M.D.

1874-1941

After many months of suffering and disability, Dean Lewis died at his home in Baltimore on Oct. 9, 1941. Although his large group of friends are saddened by his loss, they must feel that he has been released from a trying and hopeless situation. As he passes from the scene, personal memories of his character, his loyalty to his country and to his friends, as well as of his great ability as a surgeon, teacher and investigator, crowd before one. Certainly no surgeon of his generation was richer in friends, and I can think of no finer epitaph as the last bell is sounded. Honors and position came to him in generous portions, and he enjoyed and prized them; but no honor ever changed his sense of the value of the homely virtues of life, and no position ever tempted him to overlook the many friendships he had made in almost every walk of life. To the many who have shared with him his enthusiasm for sports and his love of a good game and who have experienced his infectious laugh at a good story there comes a conviction that the world is a better and happier place for having had in it their friend, Dean Lewis. He will be sadly missed by all, but his spirit and his enthusiasm for good surgery will be carried on in many parts of the country and in many medical schools by the men who were fortunate enough to have come under his tutelage.

Dean DeWitt Lewis was born in Kewanee, Ill., on Aug. 11, 1874. After receiving his A.B. from Lake Forest College and his M.D. from Rush Medical College, he interned at Cook County Hospital. From 1900 to 1903, he worked as a teacher and investigator in the department of anatomy of the University of Chicago with Bensley; during this period he did six months of graduate study at the University of Leipzig with Spalteholz. He then returned to Rush Medical College and the Presbyterian Hospital, where he quickly gained a reputation as an inspiring teacher of surgical anatomy and clinical surgery and at the same time contributed a large amount of original work in the field of surgery and surgical pathology.

He recognized that it is important to the development of young men that they be given opportunities for study and investigation, and he constantly stimulated his associates. His memory of facts and people was phenomenal, and his clinics were largely attended because of his broad knowledge of the clinical subject as well as of the correlated fundamental sciences involved, which included the medicohistorical aspect. In addition to rare qualities of mind he always had the right human touch; this

was constantly in evidence in his interest in his patients and associates as persons. Such a combination is irresistible, and soon Dean Lewis not only had a large surgical practice but was much sought after as a consultant and as a speaker at medical meetings, to which he gave generously of his time and talents. In 1920 he became professor of



DEAN DEWITT LEWIS, M.D.

1874-1941

surgery at Rush Medical College and shared with Bevan the burden of teaching and directing surgical activities.

Having had many opportunities to head the departments of surgery of various medical schools, he accepted the professorship of surgery at the University of Illinois College of Medicine in 1925, but a few months later he went to Baltimore as professor of surgery in Johns Hopkins Medical School as successor to Dr. William S. Halsted. His interest

during all his years as a teacher in the development of his residents and associates has resulted in the type of training that has fitted many of them to occupy positions of importance in teaching institutions in many parts of the country.

Dean Lewis was particularly interested in the establishment of a surgical journal in which the investigative work of young surgeons throughout the country would receive early publication. He was therefore much pleased to become the first editor of the ARCHIVES OF SURGERY, which he lived to see become one of the significant surgical journals of the country. He became editor also of the widely used "Practice of Surgery," published by Prior, and at the same time edited the *International Surgical Digest*.

He was always actively interested in organized medicine and the scientific societies to which it has given rise and which have had so great an influence on the diffusion of sound knowledge. From the beginning of his career in Chicago he was an active member of the Chicago Surgical Society and the Chicago Pathological Society, and he soon became a member of many national and international organizations. Among other organizations, he was a member of the American Surgical Association, the American Association of Anatomists, the American Physiological Society, the Society of Clinical Surgery, the Interurban Surgical Society, the Southern Surgical Association, the American College of Surgeons, the Royal College of Surgeons (Ireland), the Royal Australian College of Surgeons, Società Medico-Chirurgica di Bologna, as well as an Ausserordentliches Mitglied der Deutschen Gesellschaft für Chirurgie, and a foreign member correspondent of the Société des chirurgiens de Paris. In 1933 he was President of the American Medical Association and for several years was a member of the Council on Medical Education and Hospitals. In 1933 he was made an honorary doctor of science by the National University of Ireland.

When the first World War threatened to involve the United States, Dean Lewis organized Base Hospital No. 13 at the Presbyterian Hospital, Chicago, and took it to France in May 1918. He was detached from it and made commanding officer of Evacuation Hospital No. 7. He saw much active service at Chateau-Thierry, St. Mihiel, in the Champagne and finally, just before the armistice, at Staden, Belgium. For the efficiency of his organization and the quality of his work done under difficult conditions, he was promoted to the rank of lieutenant-colonel and given the distinguished service medal by the United States government.

His life was notable and happy. He was a positive character and always took a position on questions that seemed important. His sound surgical judgment played a considerable role in promoting good surgery wherever he worked. He leaves many friends who will never forget him.

VERNON C. DAVID, M.D.

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of the report, the patient was 30 years old. Of the patients in the remaining cases, 1 was Cuban, 1 Spanish, 1 Hungarian, 1 German, 3 Italians and 4 Jews. In 93 of the other cases the patients were stated to be white. In the remainder they were presumably white and undoubtedly represented American, English, German, French and Russian nationality, as judged by the nationality of the authors.

Sex.—The sex of the patient was given in 156 cases, in which 78 patients were male and 78 female, an equal division.

Distribution or Location of the Nevus.—In 154 cases the side of involvement was stated. In 79 the nevus occurred on the left side of the body, and in 75, on the right side. In the male patients the left side was affected in 37 cases and the right side in 39 cases; in the female patients the left side was affected in 40 instances and the right side in 31. In short, in this series of cases there was equal involvement of the sexes; almost equal involvement of the two sides of the body in the group as a whole, and equal involvement of the two sides of the body in each sex. In 14 of the cases the nevus crossed the midline, but in no case was there sufficient crossing to mar the predominantly unilateral distribution.

For purposes of classifying the distribution of these nevi the body was arbitrarily divided into twelve portions: face and head, neck, axilla, shoulder, arm, forearm, hand, trunk, genitalia, thigh, leg and foot. The number of times each of these areas was involved in the 156 cases in this series is as follows: face and head, 40; neck, 55; axilla, 39; shoulder, 46; arm, 54; forearm, 37; hand, 26; trunk, 108; genitalia, 28; thigh, 59; leg, 42; and foot, 29. In 27 cases only one of these areas was involved: trunk, 11; face and head, 8; neck, 5, and thigh, shoulder and foot, 1 each. Two areas were involved in 33 cases. In 11 cases the lesions were limited to the face and neck; in 6 to the axilla and trunk; in 4 to the neck and trunk and to the trunk and thigh, respectively; and in 1 each to the axilla and shoulder, the arm and trunk, the genitalia and thigh, the neck and shoulder, the thigh and leg, the shoulder and trunk, the leg and foot and the face and trunk. In 34 cases three areas were involved, with no single outstanding group of areas. In 20 cases four areas were involved; in 14 cases, five areas; in 14 cases, six areas; in 5 cases, seven areas, and in 7 cases, eight areas. Of the 2 cases in which nine areas were affected, the face, neck and shoulder were spared in 1 and the axilla, shoulder and forearm in the other. In 1 case all areas were included except the hand and foot; in another only the hand and leg were omitted, and in 2 the lesions covered all areas.

In summary, the nevi in 94 of the cases, or 60.2 per cent of the series, were limited to three areas or less. In 22 cases they were limited to the head and neck; in 7 cases, to the upper extremity; in 5 cases, to the

lower extremity; in 17 cases, to the trunk alone (including the axilla); in 15 cases, to the trunk and upper extremity, and in 21 cases, to the trunk and lower extremity. There was no single area or group of areas of distribution which was sufficiently outstanding to indicate a single pattern of pathogenesis. However, the lesions of the trunk were arranged generally in a curving transverse band, except near the midline anteriorly or, less often, posteriorly, where the typical arrangement was in a vertical band sharply limited by the median line. The lesions of the extremities were almost always arranged in longitudinal streaks, often running a slightly spiral course. Nevi affecting the genitalia were sharply limited at the median line.

In several cases there were peculiarities of distribution. In Sequeira's case,³⁴ that of a pigmented nevus appearing at birth, distributed on the left side of the face, head and neck of a girl, showed involvement of the mucosa of the lip, buccal mucosa, gums and soft palate. Evans³⁵ also presented a case in which the lips, tongue and tonsils were affected. The lesion was a more extensive nevus, occurring in a male, limited to the left side of the body and including the face, head, arm, forearm, hand and trunk. Tobias³⁶ presented a case of a pigmented nevus, also of the left side of the face, head and neck of a girl, and appearing at birth, which likewise involved the left side of the tongue and the buccal mucosa. The patient also had partial hemiatrophy of the left upper and lower extremities. Two other cases in which there was intraoral distribution are that of Simon,³⁷ in which the hard palate, left tonsil and pharyngeal wall were affected, and that of Waelsch,³⁸ in which there was extension to the mucous membrane of the lower jaw and left cheek. Simon's patient was a girl with a pigmented nevus on the left side, limited to the head; Waelsch's patient was a male who had a pigmented nevus of the left side of the head and neck, dating from birth.

It is a strange coincidence, perhaps, that in all 5 of these cases the nevus was on the left side and that in 4 of them it was limited to the face, head and neck.

34. Sequeira, J. H.: Case of Naevus Unius Lateris of Skin and Mucous Membrane, *Brit. J. Dermat.* **24**:313, 1912; *Proc. Roy. Soc. Med. (Sect. Dermat.)* **5**:201, 1911-1912.

35. Evans, W.: Case of Extensive Naevus, *Brit. J. Dermat.* **14**:263, 1902.

36. Tobias, N.: Nevus Unius Lateris, with Unilateral Hemiatrophy of the Left Side of the Body, *Arch. Dermat. & Syph.* **15**:83 (Jan.) 1927; Congenital Hemiatrophy Associated with Linear Naevus: Case, *Arch. Pediat.* **45**:673, 1928; Extensive Linear Nevus with an Associated Hemiatrophy, *Arch. Dermat. & Syph.* **18**:451 (Sept.) 1928.

37. Simon, T.: Ueber Nerven-Naevi, *Arch. f. Dermat. u. Syph.* **4**:24, 1872.

38. Waelsch, P.: Systematisierter ichthyosiformer Naevus, *Arch. f. Dermat. u. Syph.* **114**:237, 1912.

Age Incidence.—In 74 of the cases (46.3 per cent) the nevus was present at birth or appeared shortly thereafter. In 9 it appeared during the first year, and in 9, between the age of 1 and 2 years. One nevus appeared at 2 years of age; 4 at 3 years; 3 at 5 years; 2 at 8 years; 2 at 9 years; 1 at 12 years; 3 at 14 years; 1 at 16 years, and 2 at 17 years. In 1 patient the nevus appeared at the age of 46; this was a patient of Balzer and LeCornu.³⁹ The patient was a 47 year old man at the time of presentation and exhibited a right unilateral nevus of light brown pigmentation which was present on the neck, trunk, thigh and leg and was accompanied with no subjective symptoms.

In 13 instances, the nevi appeared at some time during childhood. In the remaining 35 the age of incidence was not given, but the upper limit of the possible age incidence may be deduced from the age of the patient at the time of presentation. In 11 the patients were below the age of 20, in 11, below 30 and in 5, above 30. In 8 cases neither the age of incidence nor the age of presentation was given.

A review of the ages of the patients at the time of presentation showed marked preponderance of the younger groups. Six patients were below the age of 1 year; 31 patients were less than 10 years of age; 47 patients were between 10 and 20; 37 were between 20 and 30; 14 were between 30 and 40; 7 were more than 40, and in 14 instances the age at the time of presentation was not stated.

Of the 7 patients over 40 years of age, 1 has already been mentioned. Of the remainder, 1 was presented by Okamura²³; he was a 45 year old white man who exhibited a nevus on the right side, confined to the trunk, which appeared in childhood. Lasser's patient⁴⁰ was a woman 52 years of age whose lesion had appeared at birth, was limited to the right side of the body, was lightly pigmented and involved the axilla, arm, forearm, trunk, thigh and leg. The patient of Grütz⁴¹ showed a nevus affecting the leg and foot, present at birth in a man who was 60 years old at the time of the report. Gerhardt's patient²² was a 61 year old man who had been affected from birth by a pigmented nevus involving almost the entire right side of the body. In many areas this nevus was not pigmented. Jadassohn's patient^{22a} was a 66 year old man with a nevus limited to the right thigh and the right side of the trunk; Luneau's⁴² patient was a 45 year old man with a pigmented nevus limited to the right side of the trunk.

39. Balzer, P., and LeCornu, P.: Contribution clinique à l'étude des dermatoses. *Ann. de dermat. et syph.* 2:929, 1901.

40. Lasser: Zur Therapie des Naevus verrucosus. *Arch. f. Dermat. u. Syph.* 33:202, 1895.

41. Grütz: Psoriasis disseminata et verrucosa et linearis. *Naevus verrucosus*. *Zentralbl. f. Haut- u. Geschlechtskr.* 56:230, 1937.

42. Luneau, H. G.: Des naevi systématisés. *Thesis, Paris, no. 56, 1919.*

Three patients showed peculiarities of onset of the nevus. In Sibley's patient,⁴³ a nevus affecting the axilla, shoulder, arm and trunk of an 18 year old girl appeared at the age of 5 years, following scarlet fever. Little's patient,⁴⁴ a 6 year old girl, at the age of 3 years had a "fit" followed by paralysis of the right leg. Three weeks later a pigmented nevus appeared on the left arm, axilla and trunk and remained unchanged until the time of presentation. In Geber's patient⁴⁵ a pigmented nevus appeared on the trunk and axilla six months after the patient was kicked by a cow. The injury caused periostitis and necrosis of bone, necessitating the removal of several fragments of bone from the ribs. It is doubtful whether these occurrences had more than a coincidental relation.

Heredity.—In 123 cases occurrence of nevi in the family was not mentioned. In 33 cases it was stated that there was no such occurrence. In only 4 cases was there any evidence of a hereditary factor. In the case of Samuel⁴⁶ the patient was a 26 year old woman who at the age of 16 had first noticed flat, warty lesions appearing on the chest and axilla. At the age of 25 the nevus began to appear on the neck and forearm. Her daughter, aged 9, was beginning to show similar nevi in the same location. The patient of Lesné, Clément and Boquien⁴⁷ was a 7 year old boy with a pigmented nevus on the left side, involving the arm, forearm, hand, trunk, thigh and leg, whose mother had also had a *keratose*. However, nothing further was known about her, because she had died. Omens⁴⁸ presented a 6 year old Jewess who had a pigmented nevus on the left side, involving the arm, trunk and thigh. Her mother had a large pigmented nevus involving the extensor surface of the left arm. Winkler's patient⁴⁹ was a 13 year old girl with a pigmented nevus appearing at the age of 6 months on the left thigh, leg and trunk.

43. Sibley, W. K.: Presentation of a Case of Naevus Unius Lateris with Unusual Effects of Solid Carbon Dioxide (*Dermatitis Repens*), *Brit. J. Dermat.* **25**:234, 1913; *Proc. Roy. Soc. Med. (Sect. Dermat.)* **6**:159, 1912-1913.

44. Little, G.: *Naevus Zosterformis*, *Brit. J. Dermat.* **17**:181, 1905.

45. Geber, cited by Neumann, I.: *Ueber Naevus papillaris (Thompson) neuroticus, unius lateris (v. Bärensprung), neuropathisches Hautpapillom (Gerhardt), Nervennaevus- (Th. Simon), Oesterr. Jahrb. f. Pädiat.* **8**:165, 1877.

46. Samuel, H. C.: A Case of Linear Naevus in a Mother and Child. *Proc. Roy. Soc. Med. (Sect. Dermat.)* **8**:126, 1914-1915.

47. Lesné, E.; Clément, R., and Boquien, Y.: *Naevus hyperkératosique verruqueux et pigmentaire à disposition zoniforme*, *Bull. Soc. de pédiat. de Paris* **30**: 448, 1932.

48. Omens, D. V.: *Nevus Unius Lateris*, *Arch. Dermat. & Syph.* **37**:922 (May) 1938.

49. Winkler: Fall von systematisiertem Naevus, *Schweiz. med. Wchnschr.* **51**: 137, 1921.

One brother had a yellow nevus on the right cheek, and her grandmother had a benign nevus on the leg which became malignant and caused her death.

Leven⁵⁰ presented the case of a young man with an extensive bilateral pigmented linear nevus of the trunk. Because of its bilateral distribution the nevus is not included in this study, but it is interesting from the point of view of heredity. The same lesion with the same distribution was presented by 2 older sisters. The remaining 6 siblings were not affected. Another interesting example of familial incidence not included in the study was cited by Bardach.⁵¹ Identical female twins each had systematized, pigmented, bilaterally distributed nevi of the face, thorax and lower extremities. The lesions appeared simultaneously in the twins twenty-two months after birth.

Pigmentation.—Of the 156 nevi, 112 exhibited some degree of gross pigmentation which varied in degree from light yellow to dark brown or black. This pigment is largely exogenous, i. e., dirt, which invariably and inevitably accumulates in the papillary clefts of the tumor. In those regions where the tumor is constantly moistened with sweat, such as the axillas, groins, palms and soles, it assumes a pinkish white complexion, utterly devoid of traces of pigmentation. Under the microscope there is no increased pigmentation of the basal epithelial layer. The number of melanoblasts is not noticeably greater than normal, and true neval cells are absent. These facts are in accordance with the observation that the malignant derivatives of naevus unius lateris are either basal cell or squamous cell epitheliomas and not melanoma as might be supposed.

Relation to Nerve Distribution.—In 53 of the collected cases the tumors were considered by the authors to exhibit a configuration corresponding to the distribution of nerves. Two of the tumors were thought to follow cranial nerves; 25 were said to bear a distinct relation to spinal segments, and 20 were described as occurring along the cutaneous connections of peripheral nerves. Six tumors were believed to follow the lines of Voigt. Two tumors were thought to be related to cutaneous faults and one to follow hair lines. To the remaining (87) tumors no pattern of configuration could be applied.

In our own 4 patients the only peculiarity of distribution was that the nevi were arranged in a segmental manner. At first glance this would seem to agree with spinal nerve distribution. However, on close comparison of the distribution of the nevi with the course of the central and peripheral nerves, no constant agreement could be found in any case.

50. Leven: *Naevus linearis atrophicus et depigmentosus*, Arch. f. Dermat. u. Syph. **140**:403, 1922.

51. Bardach, M.: *Systematisierte Naevusbildungen bei einem eineiigen Zwillingpaar*: Ein Beitrag zur Naevusätiologie, Ztschr. f. Kinderh. **39**:542, 1925.

The nevus of patient 1 covered an area innervated by the eighth cervical nerve, the first, fourth, fifth, sixth, seventh, eighth, ninth, tenth, eleventh and twelfth thoracic nerves and the first, second, third and fourth lumbar nerves. However, none of the areas was concurrent with a single zone of innervation, and no margins of the nevus corresponded to the boundary of distribution of the spinal nerves. The nearest approximation occurred in the distribution of the lesions of the forearm and hand (fig. 1 C). Here the streak on the forearm closely followed the course of the medial antebrachial cutaneous nerve (eighth cervical, first thoracic). From the wrist and over the palm of the hand and the volar aspect of the fourth and fifth fingers the distribution closely approximated that of the sensory branches of the ulnar nerve (also eighth cervical and first thoracic). However, here the analogy stopped, because the nevus extended medially to involve the medial aspect of the fourth finger and the lateral aspect of the third, an area supplied by the median nerves (fifth, sixth, seventh and eighth cervical).

In case 2 the nevus covered an area innervated by the eighth cervical nerve and the first, second, third, fourth, fifth, sixth, seventh and eighth thoracic nerves. In case 3 the area of distribution of the second, third, fourth, fifth and eighth cervical nerves, the first to twelfth thoracic nerves, the first, second and third lumbar nerves and the first and second sacral nerves was involved. In neither of these cases was there correspondence between the course of the nerves and the distribution of the nevus.

The correlation of nerve and nevus distribution was most suggestive in case 4. Anteriorly, the superior margin of the lesions of the trunk and arm coincided with the upper boundary of cutaneous distribution of the second thoracic nerve and inferiorly with the lower margin of cutaneous distribution of the twelfth thoracic nerve. However, between these points, except for their direct extension, there was little correlation between the bands of nevi and the cutaneous nerve segments. Posteriorly even the upper and lower limits did not correspond. The inferior patch extended over the distribution of the first, second and third lumbar nerves, and the upper portion of the nevus was irregularly scattered over the area of the fourth, fifth and sixth cervical nerves. The patch on the anterior aspect of the neck was in the region of the second and third cervical nerves and that in the frontal region in the area innervated by the trigeminal nerve.

In summary, no satisfactory correlation between nerve distribution and nevus distribution could be demonstrated in our 4 patients. Neither was there any occurrence with Voigt's lines or with any other known line.

Histopathologic Appearance.—The microscopic picture is surprisingly uniform. The most typical changes are marked hyperkeratosis, paraker-

atosis and slight acanthosis of the epidermis, with or without edema of the epithelial layers; increased thickness of the stratum granulosum and stratum spinosum; irregular elongation of the papillae, and round cell infiltration of the papillary layer and the corium. Hasselmann⁵² and Matras⁵² noted dilatation of blood and lymph vessels, and Morrow² only dilatation of lymphatics. Okamura⁵³ found numerous melanoblasts in the papillary layer. Callomon⁵³ and Polland⁵⁴ saw proliferation of sebaceous glands. In only 2 cases were nests of so-called nevus cells described (Ehrmann⁵⁵ and Polland⁵⁶). These occurred in the papillary layer and in the corium. One section was thought by Becker and Obermayer⁵⁷ to resemble keratosis follicularis. Adamson⁵⁸ found a large vessel and nerve running in the subpapillary plexus, which he considered significant.

Microscopic sections of our tumors showed no marked variation from the pictures described by other authors. Papillary projection and convolution of the epidermis with distortion and elongation of the dermal papillae were striking and constant features. Hyperkeratosis was also marked. Edema of the epithelial layers was not pronounced, but there was marked variation in their thickness. In one or two sections rows or groups of cells extended from the basal epithelial layer into the corium and resembled nevus cells (fig. 3). The constant absence of groups of neval cells in these tumors is an important characteristic, distinguishing them from other true nevi. The tumor process therefore is essentially a congenital papillomatosis. Occasionally dense infiltrations of plasma cells and lymphocytes were seen in the corium. In none of the specimens was there increased pigmentation of the basal epithelial layer. The pigment of these lesions was apparently exogenous and could be seen in the overlying keratin. No changes were observed in the blood or lymph vessels.

Symptoms.—Only 14 patients in this collective review were reported to have any subjective symptoms. The most common complaint was

52. Matras: Naevus linearis unilateralis systematicus, Zentralbl. f. Haut- u. Geschlechtskr. **32**:181, 1930.

53. Callomon, F.: Systematisierter Naevus mit strichformigem Verlaufe in der Medianlinie, Arch. f. Dermat. u. Syph. **101**:221, 1910.

54. Polland, R.: Naevus linearis verrucosus, Dermat. Ztschr. **20**:499, 1913.

55. Ehrmann: Fall von systematisiertem Naevus, Arch. f. Dermat. u. Syph. **67**:282, 1903.

56. Polland, R.: Zur Lokalisation und Histologie der systematisierten Naevi, Arch. f. Dermat. u. Syph. **102**:101, 1910.

57. Becker, S. W., and Obermayer, M. E.: Nevus Unius Lateris, with a Microscopic Picture Resembling Keratosis Follicularis, Arch. Dermat. & Syph. **37**:102 (Jan.) 1938.

58. Adamson, H. G.: The Histology of a Case of Linear Naevus, Brit. J. Dermat. **18**:235, 1906.

itching, which occurred in 8 patients. In the patients of Hufschmitt⁵⁹ and Heidingsfeld³ the itching was mild. In those of Fox,⁶⁰ Omens⁴⁸ and Lindenheim²⁸ the degree of discomfort was not noted. The remaining 3 patients suffered from severe itching. In Parkhurst's patient⁶¹ the itching was constant, and secondary impetigo resulted from the scratching; Lane's⁶² patient and Morrow's² patient suffered from severe itching, particularly after bathing. One boy, aged 5, presented by Wegge,⁶³ had "indefinitely described painful sensations." Barham's patient⁶⁴ complained of irritation of the face when shaving and irritation of the thigh and scrotum in hot weather. In the patient of Mackenzie⁸ the lesions were irritable at night and caused marked scratching. The patient of Reckzeh,⁶⁵ a 12 year old boy with a nevus involving the axilla and trunk, suffered discomfort from the axillary portion being soft and moist. Another nevus of similar location (Frankovic⁶⁶) caused a strong fetor. Finally, the patient of Ullmo,⁶⁷ a 20 year old woman with a pigmented nevus situated on the right side of the face, experienced a feeling of warmth on the affected side, although objectively there was no difference as compared with the left side. From this summary it seems evident that when symptoms occur at intervals in patients with these tumors, they are generally due to complications, such as infection, laceration and maceration by sweating.

Treatment.—The experience of any one physician, whether a dermatologist, a radiologist or a surgeon, has been so limited that no uniform or accepted plan of treatment has been devised. Thus, in reviewing this group of case reports, many bizarre forms of therapy have been employed without satisfactory results. For example, Sézary, Lefèvre and Rondinesco⁶⁸ gave eight autoinjections of blood, with supposed partial fading

59. Hufschmitt, G.: Vaste naevus de l'hémithorax et du bras gauche, Bull. Soc. franç. de dermat. et syph. **33**:305, 1926.

60. Fox, C.: Linear Naevus Papillaris, Brit. J. Dermat. **19**:258, 1907.

61. Parkhurst: Pruritic Nevus Unius Lateris, Arch. Dermat. & Syph. **14**: 625 (Nov.) 1926.

62. Lane: Nevus Unius Lateris, Arch. Dermat. & Syph. **18**:455 (Sept.) 1928.

63. Wegge, W. F.: A Case of Naevus Unius Lateris, Milwaukee M. J. **5**:191, 1897.

64. Barham, C. R.: Report of a Case of Naevus Unius Lateris, M. Rec. **43**: 200, 1893.

65. Reckzeh: Zwei Falle von Naevus linearis unius lateris, Charité-Ann. **27**: 173, 1903.

66. Frankovic: Naevus pigmentosus papilliferus unilateralis systemisatus, Zentralbl. f. Haut- u. Geschlechtskr. **50**:354, 1935.

67. Ullmo, A.: Vaste naevus pigmentaire ardoisé de la moitié droite de la face, Bull. Soc. franç. de dermat. et syph. **40**:1516, 1933.

68. Sézary, A.; Lefèvre, P., and Rondinesco: Naevus pigmentaire linéaire, apparu à la puberté et évolutif: Action de l'autohémothérapie, Bull. Soc. franç. de dermat. et syph. **38**:651, 1931.

of a pigmented naevus unius lateris of the arm and forearm. Parenteral administration of arsenic has been resorted to empirically by Fordyce,⁶⁹ Lindenheim²⁸ and Plonski,¹⁰ without lasting benefit. Strasser⁷⁰ used thyroid tablets, without improvement. It must be evident from the nature of the disease that medical measures which are accepted for the various keratoses and dermatoses will not be successful, as the lesion involves the entire thickness of the integument.

The aim of treatment is to remove the linear papillary nevus in its entirety and by so doing to overcome the cosmetic blemish it causes and to avoid the hazards of possible future malignant degeneration. In our opinion the only way to achieve this end result successfully is surgical excision and plastic repair either by undermining the skin sufficiently to effect primary wound closure by sliding flaps (case 2) or by skin grafting (case 3). This plan of treatment has been advocated by Alexander,⁷¹ Calloman,⁵³ Galewsky and Schlossmann,⁷² Gerhardt¹¹ and others. Earlier attempts at curettage were made, which removed the bulk of the tumor; recurrence inevitably followed because the basal layer of the skin persisted (Bleiman⁷³; Ransom⁷⁴). The application of solid carbon dioxide or cryotherapy has been suggested by numerous authors, among them Fordyce,⁶⁹ Gaskill,⁷⁵ Hufschmitt,⁵⁹ Little,⁷⁶ Roop⁷⁷ and Sibley.⁴² Freezing causes the excessive papillomatous structure to slough off, leaving a cleaner base, but the improvement is only temporary.

Roentgen and radium therapy are never completely successful, although some improvement results with flattening of the nevus. Irradiation readily removes other varieties of hyperkeratosis and papillomatosis because of their superficial character; in the case of naevus unius lateris, however, the entire integument is involved. Radium or roentgen irradiation therefore can ameliorate but cannot cure this condition unless given to the degree of actual cauterization. The nevus involving the skin over the left breast of 1 of our patients (case 1) received roentgen

69. Fordyce: Naevus Verrucosus Linearis, *J. Cutan. Dis.* **37**:250, 1919.

70. Strasser, P.: Beitrag zur Kenntnis der systematisierten Naevi, *Arch. f. Dermat. u. Syph.* **66**:21, 1903.

71. Alexander, A.: Fall von Naevus linearis unius lateris, *Dermat. Ztschr.* **2**:343, 1895.

72. Galewsky, E., and Schlossmann, A.: Ueber Naevus linearis, *Deutsches Arch. f. klin. Med.* **58**:85, 1896.

73. Bleiman, A.: Naevus linearis, *J. Cutan. Dis.* **26**:279, 1908.

74. Ransom, C. J.: Unusual Case of Naevus Unius Lateris, *J. Cutan. & Genito-Urin. Dis.* **14**:141, 1896; abstracted, *Arch. f. Dermat. u. Syph.* **45**:280, 1898.

75. Gaskill: Naevus Pigmentosus Unius Lateris, *J. Cutan. Dis.* **34**:232, 1916.

76. Little, G.: Two Cases of Naevus Unius Lateris, *Brit. J. Dermat.* **23**:83, 1911; *Proc. Roy. Soc. Med. (Sect. Dermat.)* **4**:64, 1910-1911.

77. Roop, W. O.: Naevus Verrucosus—Ichthyosis Hystrix, *Arch. Dermat. & Syph.* **37**:131 (Jan.) 1938.

therapy when she was 13 years of age; when she was 23 years old a true mammary carcinoma had developed in the same breast. This sequence of events may have been coincidental. The various authors who have used roentgen rays and radium are Fox,⁷⁸ Frankovic,⁶⁶ MacKee and Wise,⁷⁹ Sequeira,³⁴ and Tobias.³⁶

Electrofulguration, electrodesiccation or surgical endothermy, with either the monopolar or bipolar coagulating or the cutting current, has had popular usage (Callomon⁵³; Heidingsfeld³; Weissenbach, Lévy-Franckel and Carlu⁸⁰). The method is inferior to sharp surgical excision unless the endotherm knife is used to remove the entire thickness of the tumor and the procedure is followed by surgical repair, i.e., suturing. Electrocoagulation, even when successful, is too frequently followed by excessive keloidal scarring.

Course of the Disease.—Unfortunately, the ultimate outcome in any case in this series was not given. The majority of the lesions remained stationary. Some tumors became more widespread after their initial appearance. The tumor in Frankovic's case,⁶⁶ which had been stationary since birth, began to show extension at the age of 22. A few tumors showed partial spontaneous regression, in 1 instance with subsequent recurrence (Heidingsfeld³). Only one of the nevi presented showed complete spontaneous disappearance without treatment. This patient, described by Bettmann,⁸¹ was a normal boy, born at term. On the second day after birth he presented a systematized linear warty nevus involving the left side of the trunk (sharply demarcated at the median line) and the left arm and forearm. On the eighth day the horny character of the lesion was more pronounced; at reexamination, one month after birth, the lesion had spontaneously disappeared except for a short line on the forearm and an S-shaped line on the abdomen. Six months later every trace had disappeared. Koren's patient,⁸² on whom the data were insufficient to justify inclusion in this series, showed spontaneous disappearance of the lesion. The patient was a boy 9 months old who at birth had a nevus involving the right forearm and hand. Grütz's patient⁴¹ had a basal cell carcinoma in the region of the lesion on the thigh, which recurred after removal.

78. Fox, H.: Presentation of a Case of Naevus Pigmentosus Unilateralis, Arch. Dermat. & Syph. 1:467 (April) 1920.

79. MacKee and Wise: Naevus Verrucosus Linearis, J. Cutan. Dis. 34:696, 1916.

80. Weissenbach, R. J.; Lévy-Franckel, and Carlu, L.: Naevus verruqueux géant de topographie dimidiée radicaire: Electrocoagulation des placards cervicaux et des lésions de la face, Bull. Soc. franç. de dermat. et syph. 43:406, 1936.

81. Bettmann: Spontane Rückbildung eines Naevus verrucosus unius lateris, Dermat. Ztschr. 20:473, 1913.

82. Koren, cited by Galewsky and Schlossmann.⁷²

Presence of Other Congenital Abnormalities or Unusual Features.—Gerhardt's patient ¹¹ was epileptic. Hufschmitt's ⁵⁹ patient lacked the lobe of an ear and had malformation of the teeth. The patient of Brocq and Rivet ⁸³ evidenced more marked development of hair on the affected side of the body. Camptodactylia was present in the patient reported on by Sézary, Lefevre and Rondinesco.⁶⁸ Galloway ⁸⁴ presented a patient with a nevus affecting the left side of the scalp and neck. There was imperfect formation of the outer canthus of the left eye, with incomplete separation of the cutaneous folds. The outer portions of both corneas were white. Meissner's patient ⁶ had poorer development of musculature and deficient hearing on the affected side. There was partial hemiatrophy of the upper and lower extremities on the affected side in the patient presented by Tobias,⁹⁰ and in Crocker's patient ⁸⁵ there was associated pseudohypertrophic paralysis. Adamson's patient ⁸⁶ had a supernumerary nipple. Reckzeh's patient ⁶⁵ was feeble-minded. The patient of Spiegelberg ⁸⁷ showed association with hereditary syphilis. Strasser's patient ⁷⁰ had a papilloma of the tongue. The nevus described by Spiethoff ⁸⁸ occurred on the left side of the nose; the patient had a strabismus converging left and a congenital preputial midline defect. The father also had left strabismus. Müller's patient ¹⁴ exhibited a very extensive pigmented nevus covering most of the right side of the body. The right side of the scalp, even where not affected by the nevus, was covered by thin, long, blonde hair. The hair on the left side of the head was thick and black. Lewith's patient ⁸⁹ had a tumor which involved the right side of the body. The right axilla perspired more than the left; the right half of the face was smaller; the right pupil was narrower; the nose pointed toward the right; the right breast was smaller, and the patient was left handed. The nevus in the case of Kudisch ⁹ was associated with total aplasia of the nuclei of both facial nerves.

Tobias presented a case ⁹⁰ of nevus of the right thigh associated with lymphangioma of the vulva. He stated the belief that it was the only

83. Brocq, L., and Rivet, G.: Obstruction de naevus verrucosus unius lateris, *Ann. de dermat. et syph.* 4:596, 1883.

84. Galloway: Naevus Unius Lateris, *Brit. J. Dermat.* 14:57, 1902.

85. Crocker, H. R.: A Case of Papillary Growths in the Course of the Nerves, *M. Times & Gaz.* 1:633, 1880.

86. Adamson, H. G.: A Case of Unilateral Pigmentary Naevus, *Brit. J. Dermat.* 23:77, 1911.

87. Spiegelberg: Ueber einen Fall von angeborener papillomatöser sogenannter neuropathischen Wartzenbildung, *München. med. Wchnschr.* 43:695, 1896.

88. Spiethoff: Strichformiger Naevus verrucosus, *Zentralbl. f. Haut- u. Geschlechtskr.* 18:830, 1925-1926.

89. Lewith, R.: Ueber einen Fall von Naevus pigmentosus mit homolateralen nervösen Störungen, *Arch. f. Dermat. u. Syph.* 154:69, 1927.

90. Tobias, N.: Lymphangiectatic Hypertrophy of the Vulva Occurring in a Nevus Unius Lateris, *Arch. Dermat. & Syph.* 8:647 (Nov.) 1923.

case of association of these two conditions on record. The patient also showed smoothness of the right side of the tongue, which was thicker than the left, and a rough, scaly condition of the lips, sharply limited at the midline. The patient of Whitelocke and Rooth,⁹¹ with a nevus affecting the left side of the trunk, the genitalia and thigh, presented in addition a fibroma of the left inguinal canal. The fibroma was removed.

Grütz's patient⁴¹ apparently had psoriasis associated with the nevus, as did the patient of Philippson.¹⁹ Adamson's patient⁸⁶ presented a pigmented papillary nevus of the left thigh and leg with a hemangioma in the same region. The hemangioma had been present at birth, but the nevus appeared later. Hallopeau and Weil⁹² also presented a case of associated vascular and hyperkeratotic nevi, but the distribution was bilateral, and so it is not included in this series.

COMMENT

A survey of the literature makes it evident that the peculiarity of unilateral distribution is not limited to nevi of the verrucous or papillary type. As has been stated by many authors, a nevus may involve any of the components of the skin. Furthermore, papillary and verrucous nevi of systematic distribution may involve both sides of the body. These facts have led many authors to assume that all nevi of linear distribution should be classified as one group and that subdivisions according to distribution or according to the microscopic pathologic data are artificial and confusing. It is our opinion, however, that papillary or verrucous nevi of linear and unilateral distribution conforming to the criteria previously enumerated form a single clinical entity that is sufficiently characteristic to deserve individual classification to the exclusion of other forms.

Naevus unius lateris is manifested most commonly in the white race. There is equal involvement of the two sexes and of the two sides of the body in each sex. Nevi of limited distribution are more common than the more extensive type. There is no marked predilection for any single portion of the body. Lesions of the trunk are most frequently arranged in a transverse manner and those of the extremities in longitudinal or spiral streaks. However, there is no one characteristic pattern of distribution. (In this series only one third of the tumors showed any relation to nerve distribution.) In only rare instances is there any evidence of a hereditary factor. Almost half of the lesions appear at or shortly after

91. Whitelocke, A., and Rooth, J.: Case of Naevus Pigmentosus and Verrucosus, Brit. M. J. 1:1027, 1902.

92. Hallopeau, H., and Weil, E.: Naevi systématisés métamériques, Bull. Soc. franç. de dermat. et syph. 8:171, 1897; Ann. de dermat. et syph. 8:483, 1897.

birth, and of the remainder the majority appear in early life. Over two thirds of the nevi show some degree of pigmentation. In some cases this is apparently due to increased pigmentation of the basal epithelial layer. In our own patients the pigment was exogenous. The microscopic picture of this type of nevus is fairly characteristic and consists chiefly of hyperkeratosis, distortion of the epidermis and elongation of the papillae. Nests of the so-called nevus cells are seldom, if ever, seen. Subjective symptoms are for the most part absent, and when they do occur they generally take the form of itching or irritation. Many forms of treatment have been employed, with varying degrees of success. We believe surgical excision of the entire thickness of the involved epidermis to be the method of choice. For extensive nevi this is necessarily done in multiple stages. Skin grafting may or may not be required, depending on the size of the area of skin removed.

The cause of the condition remains a vexing problem. The distribution of the majority of nevi shows no precise correspondence to that of central or peripheral nerves or to any of the various lines which have been described. On this basis alone, therefore, a case for causal relation to the nervous system cannot be made. In many patients, as in our own, there is segmental distribution which at first glance seems to coincide with nerve distribution; but on close analysis the relation does not hold. However, it must be remembered that there is often considerable overlapping of the peripheral terminations of separate cutaneous nerves and that segmental distribution is peculiar to the nervous (and skeletal) system in the adult human body. Furthermore, the trophic influence of nerves cannot be excluded as a factor in pathogenesis.

The pathologic process with this type of nevus appears to be located solely in the epidermis. It seems much more logical to assume that the distortion and elongation of the dermal papillae are secondary to the epithelial changes rather than their cause and therefore that the initial change occurs in the ectoderm rather than in the mesoderm.

The occurrence of skeletal malformations and epilepsy with naevus unius lateris has been interpreted by some authors as showing the relation of nevi to the central nervous system. The various coincidental malformations of the body collected from the literature and cited for the most part involved the nervous system and gave strength to this view. However, other systems besides the nervous system are involved, and, although various congenital abnormalities seem to appear more frequently in persons having nevi than in those unaffected, the possibility of mere coincidence cannot be completely discarded.

In summary, the cause and pathogenesis of naevus unius lateris are still unsatisfactorily explained. There is no universally apparent relation to the nervous system, but such a relation cannot be ruled out as the

prime etiologic factor. The microscopic and clinical pictures indicate primary involvement of the epidermis rather than the dermis.

It is generally known and has been stated many times that nevi may become malignant and that the form of malignancy which verrucous and papillary nevi take is not that of melanoma, but of epidermoid carcinoma. Tōyama and Kojima⁹³ reported a case of generalized verrucous nevi in which several basal cell epitheliomas and one squamous cell carcinoma developed. By far the majority of the patients reported on are in the younger age group. It is unfortunate that the subsequent course of these patients is not reported so that the possible relation of the lesion to carcinoma may be determined.

In our own series of 4 cases, 3 of the patients died of cancer. In 1 of them (case 3) multiple basal cell carcinomas developed in the nevus. The axillary nodes were involved by epidermoid carcinoma, presumably metastatic from some undetected primary epidermoid cancer in the papillary nevus. The patient died of pulmonary metastases.

Another patient (case 1) died at the age of 23 from pulmonary metastases of carcinoma of the breast. The breast had always been smaller than its mate, had been covered with nevi and had received heavy irradiation. When the lesion was first noted it was believed to be a cutaneous cancer and to be due possibly to the irradiation. However, the microscopic picture of mammary adenocarcinoma precluded that possibility, as far as is known at present. The comparative youth of the patient, the presence of the nevus on the breast and the small size of the breast, all unusual circumstances, arouse speculation as to a possible causal connection between the nevus and the malignant tumor.

The third patient (case 2) died of carcinoma of the esophagus and stomach at the age of 43. Although in this patient the tumor developed at a younger age than the average, there is little basis on which to assume more than coincidental occurrence of the nevus and the carcinoma.

In conclusion, it should be emphasized that the relation of naevus unius lateris to carcinoma should be more thoroughly investigated and the patients followed over a period of years to determine malignant potentiality.

Additional references will appear in the reprints of the article.

93. Tōyama, I., and Kojima, R.: A Case of Verrucous Nevi Associated with Basal Cell Epitheliomas, Bowen's Disease, and Squamous Cell Epithelioma, *Jap. J. Dermat. & Urol.* **40**:116, 1936; abstracted, *Arch. Dermat. & Syph.* **36**:626 (Sept.) 1937.

HISTOLOGIC DISTRIBUTION OF VITAMIN A IN BIOPSY SPECIMENS OF THE LIVER

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The use of the fluorescence microscope permits the histologic visualization of vitamin A in tissues.¹ The results of recent investigations on the histologic distribution of vitamin A in the livers of human beings and of animals under normal and under pathologic conditions have been reported.² In these studies the human tissues examined were obtained at autopsy. Two objections may be raised against the results: 1. Postmortem changes may influence the picture, although no evidence of changes occurring in the first twelve hours after death was obtained in animal experiments. 2. The antemortem conditions and the irregular intake of food prior to death may influence the amount and the distribution of vitamin A. The purpose of this paper is to report on a study of the vitamin A fluorescence in specimens of human livers obtained at operation in order (1) to investigate the significance of the foregoing objections, (2) to examine the influence of the known pre-operative nutritional state on the vitamin A content of the liver and (3) to evaluate the influence of hepatic function on the distribution of vitamin A when the factor of alteration of function prior to death was absent.

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From the Cook County Hospital and the Cook County Graduate School of Medicine.

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1. von Querner, F.: Der mikroskopische Nachweis von Vitamin A in animalen Gewebe. Zur Kenntnis der paraplastischen Leberzelleinschlüsse, *Klin. Wchnschr.* **14**:1213, 1935. Popper, H.: Histological Demonstration of Vitamin A in Rats by Means of Fluorescence Microscopy, *Proc. Soc. Exper. Biol. & Med.* **43**: 133-136, 1940; Vitamin A: The Distribution of Vitamin A in the Body, *J. Mt. Sinai Hosp.* **7**:119-132, 1940.

2. (a) Popper, H., and Greenberg, R.: Visualization of Vitamin A in Rat Organs by Fluorescence Microscopy, *Arch. Path.* **33**:11-33 (July) 1941. (b) Popper, H.: The Histologic Distribution of Vitamin A in Human Organs Under Normal and Under Pathologic Conditions, *Arch. Path.* **32**:766-803 (June) 1941.

Vitamin A imparts a striking green fluorescence to the lipoids which carry it, the degree of fluorescence depending on the amount of the vitamin present. The fluorescence fades within a minute, because of the destruction of vitamin A by the ultraviolet rays used in fluorescence microscopy. The substance visualized by the characteristic fluorescence is not vitamin A itself but the fats made fluorescent by vitamin A. The specificity for vitamin A of this fluorescence in sections of fixed tissues has been demonstrated by various animal experiments.^{2a}

MATERIAL AND METHODS

The patients selected for study received different types of diets. All of them consumed a known diet for at least eight days; no evidence existed for a reduced intake of vitamin A prior to this time. Two patients received 300,000 international units of vitamin A³ twenty-four hours before operation. Patients with pathologic conditions of the liver were included; hence the distribution of vitamin A in our material cannot be used to judge the amounts of vitamin A in the livers of normal persons.

Specimens of the liver were taken in 29 cases in which the organ was exposed at operation. Part of the material was fixed in solution of formaldehyde and frozen sections were cut within thirty minutes; the other portion was fixed in Carnoy's solution and embedded in paraffin for routine histologic examination. The frozen sections, unstained and stained with phosphin 3R and methylene blue, were studied under the fluorescence microscope. The former dye is a sensitive lipid stain. Methylene blue does not interfere with vitamin A fluorescence. By changing the ultraviolet filter to a ground glass filter the exact site of the fluorescence in the section stained with methylene blue could be determined in visible light.

RESULTS

Eleven of the 29 livers appeared entirely normal on gross and on routine histologic examination. The distribution of vitamin A fluorescence agreed with that in the livers obtained at autopsy.^{2b} The fluorescence was observed in the Kupffer and in the liver cells. In the latter it was seen either in fat droplets, which were demonstrable with sudan III, or in fine lipid droplets, which were demonstrable with phosphin 3R but not with sudan III. It was further seen in lipofuscin or diffusely dissolved in the cytoplasm. The vitamin A content of the liver cells paralleled that of the adjacent Kupffer cells. The distribution varied markedly in details, even in apparently normal livers. In pathologic specimens distinct variations were observed (table).

Total Amount of Vitamin A Fluorescence.—In 2 cases the vitamin A fluorescence was so marked that it could be observed with the naked eye. In both cases a large dose of a concentrate of vitamin A was administered a day before operation. The fluorescence was evenly distributed between the liver and the Kupffer cells (fig. 1 A). In the

3. The concentrate of vitamin A used was supplied by the Abbott Laboratories

Results of Fluorescence Microscopic Studies and Routine Histologic Studies on Biopsy Specimens of the Liver Correlated with the Clinical Diagnosis

Diagnosis	Jaundice	Nutritional State	Interval Between Last Intake of Food and Operation, Hours	Damage of Liver Parenchyma	Pathologic Condition of Periportal Fields	Toxic Evidences	Total Fluorescence of Vitamin A	Hemogenic Distribution of Vitamin A	More Vitamin A in Kupfer Cells than in Liver Cells	More Vitamin A in Kupfer Cells	Lipoids Free of Vitamin A
Chronic cholecystitis and cholelithiasis.....	—	Obese	12	—	—	—	+	—	—	—	—
Calcification of gallbladder.....	—	Good	12	—	—	—	++	+	—	—	—
Cholelithiasis	—	Good	24	—	—	—	+++	+	—	—	—
Chronic cholecystitis	—	Good	18	—	—	—	+	—	—	—	—
Metastasis of pancreatic carcinoma to liver	++	Poor	20	+	+	—	+	—	—	—	—
Chronic cholecystitis; diabetes mellitus.....	—	Obese	36	±	±	—	+	—	—	—	+
Carcinoma of stomach.....	—	Poor	2 days	+	—	—	±	—	—	—	—
Chronic cholecystitis	—	Poor	4 days	—	++	—	++	+	—	—	—
Cholangitis	+	Fair	24	—	++	—	++	+	—	—	—
Carcinoma of stomach.....	—	Poor	10 days	—	+	—	++	—	—	—	+
Chronic cholecystitis	—	—	±	+	++	—	—	—	—
Chronic cholecystitis; perlobular cirrhosis..	—	Good	24	+	++	—	+	—	—	—	—
Cholelithiasis and cholelithiasis.....	±	Good	24	—	±	—	+	—	—	—	—
Cholecystitis and cholelithiasis.....	—	Obese	24	—	—	—	++	+	—	—	—
Cholelithiasis	—	Good	24*	—	—	—	++	+	—	—	—
Chronic cholecystitis	++	Fair	16	±	+	—	++	+	—	—	—
Fibrosis of gallbladder.....	—	Poor	24*	—	±	—	+	—	—	—	+
Chronic cholecystitis; diabetes mellitus....	—	Good	24	—	—	—	++	+	—	—	+
Chronic cholecystitis and cholelithiasis; diabetes mellitus	—	Good	24	—	—	—	++	+	—	—	+
Penetrating peptic ulcer.....	—	Poor	36	—	—	—	+	—	—	—	—
Cyst of liver.....	—	Poor	12	+	±	—	++	+	—	—	+
Carcinoma of stomach.....	—	Good	10	—	—	—	+	—	—	—	—
Cholelithiasis	±	Poor	8 days	—	++	—	++	—	—	—	—
Chronic cholecystitis and cholelithiasis.....	—	Good	24	—	—	—	++	—	—	—	—
Toxic hepatitis	+++	Poor	20	—	—	—	++	—	—	—	—
Carcinoma of ampulla of Vater.....	+++	Fair	17	+	++	—	+	—	—	—	—
Stone in common duct.....	+++	Fair	12	+	+	—	+	—	—	—	—
Carcinoma of pancreas.....	+++	Good	24	+	+	—	+	—	—	—	—
Hydrops of gallbladder; parenchymatous hepatitis.....	+++	Good	24	+	+	—	+	—	—	—	+
.....	—	Obese	24	++	±	+	+	—	—	—	+

* The patient received 200,000 international units of vitamin A twenty-four hours before operation.

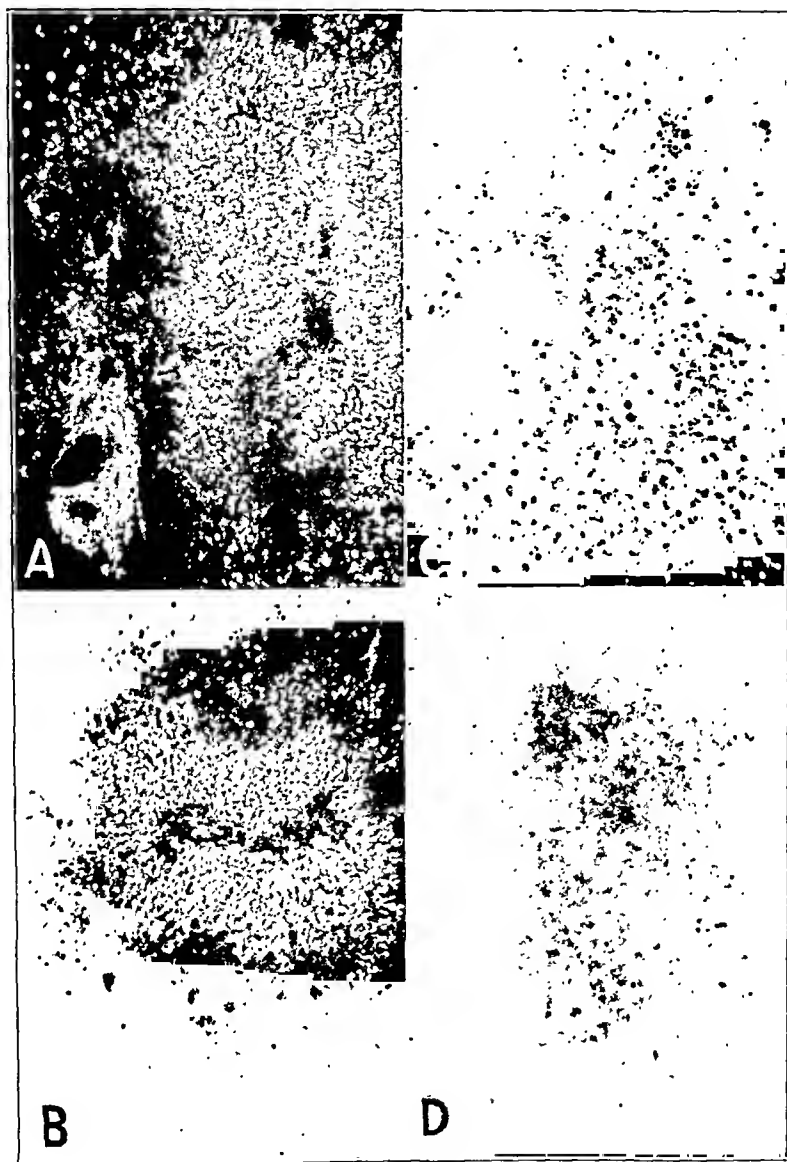


Fig. 1.—Fluorescence photomicrographs: *A*, liver with abundance of vitamin A fluorescence after oral intake of 300,000 international units of vitamin A twenty-four hours before operation. The Kupffer cells reveal high amounts of the fluorescence, and the liver cells contain many fine fluorescing droplets. *B*, liver showing strong vitamin A fluorescence imparted by the Kupffer and the liver cells, especially in the center of the liver lobule. *C*, liver showing average vitamin A fluorescence imparted by the Kupffer cells and by fine lipoid droplets and lipofuscin in the liver cells. *D*, traces of vitamin A fluorescence imparted chiefly by the Kupffer cells.

former it was imparted by fine lipoid droplets, which crowded the epithelial cells.

In 3 cases there were relatively large amounts of vitamin A fluorescence (fig. 1 *B*). The patients were in a good nutritional state. No damage to the parenchyma of the liver was apparent. In 1 case, in which there was subsiding jaundice, slight lymphocytic infiltration of the periportal fields was evident.

None of the 11 livers with average amounts of vitamin A fluorescence showed any pathologic change in the intralobular parenchyma (fig. 1 *C*). In 5, changes in the periportal fields, such as lymphocytic or leukocytic infiltrations, fibrosis or even moderate proliferation of the bile ducts, were observed. In 1 case there was slight jaundice. In most cases the liver cells were lined by fine lipoid droplets which imparted vitamin A fluorescence. The nutritional state of 5 patients was poor, as indicated by loss of weight and emaciation. Three had received no food containing vitamin A for four, eight and ten days, respectively, prior to operation, while they were fed intravenously.

Of 12 livers with small amounts of vitamin A fluorescence, 10 showed signs of damage to the parenchyma, such as central necrosis or necrobiosis, or necrosis of isolated liver cells. In 1 case there was perilobular cirrhosis with proliferation of the bile ducts and regeneration of the liver cells. Endothelial cells in the enlarged periportal fields imparted vitamin A fluorescence which is characteristic in cases of compensated cirrhosis^{2b} (fig. 2 *A*). One liver showed definite parenchymatous hepatitis with fatty infiltration and dissociation of the liver cell cords. In 6 cases there was fully developed jaundice. In the area of hepatic damage the vitamin A fluorescence of the liver cells was completely absent, in contrast to its presence in the cells of the uninvolved parts of the liver lobule. The nutritional state of 2 of the 12 patients was poor. All 12 patients took food within thirty-six hours prior to operation.

Traces of vitamin A fluorescence were found in the liver of a patient who had carcinoma of the stomach with emaciation (fig. 1 *D*). Signs of hepatic damage were present.

No influence of age or of the type of anesthesia on the distribution of vitamin A was apparent.

Relation Between Fluorescence of Kupffer Cells and That of Liver Cells.—A characteristic picture of large amounts of vitamin A fluorescence in the Kupffer cells and reduction or absence of fluorescence of the liver cells may be seen either in the entire lobule or in part of it (fig. 2 *B*). Of the 13 cases in which it was encountered, the amount of fluorescence in general was not reduced in 3, in 2 of which diabetes mellitus was present and in 1 toxic edema. Among the other cases in which there was little vitamin A fluorescence were 6 in which there was

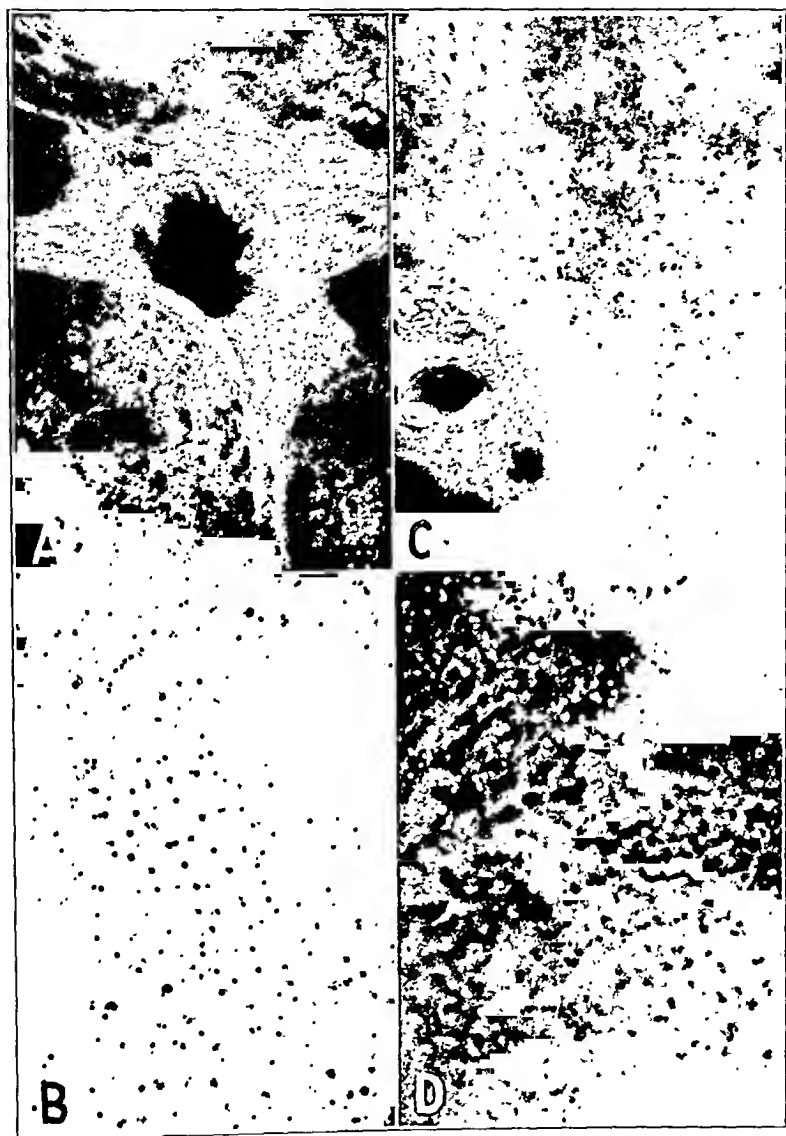


Fig. 2.—Fluorescence photomicrographs: *A*, periblobular cirrhosis. The little vitamin A fluorescence is imparted chiefly by the Kupffer cells. (The connective tissue of the proliferated periportal field gives a strong, nonfading blue fluorescence which appears white in the photomicrograph.) *B*, toxic edema of the liver. The Kupffer cells are rich in vitamin A fluorescence, while the liver cells are free of the vitamin A. *C*, jaundice. The area around the periportal field is free of vitamin A. In the intermediary zone the liver cells are free of vitamin A fluorescence, while the Kupffer cells contain a normal amount of vitamin A. *D*, diabetes mellitus. The Kupffer cells are rich in vitamin A fluorescence. The liver cells show small amounts, especially in lipofuscin.

fully developed jaundice. No influence of the nutritional state or of the interval since the last intake of food was apparent.

In 3 livers the Kupffer cells were poor in vitamin A fluorescence and there were normal amounts in the liver cells; in 2 of these the last food was taken four and eight days, respectively, before operation.

Distribution of Fat.—Usually, all lipid droplets of the liver showed vitamin A fluorescence of varying degree. The amount of the fluorescence corresponded normally, therefore, with the amount of fluorescence produced by staining with phosphin 3R. Lipoids without vitamin A fluorescence were noted in 9 instances; they were especially evident in 1 case of parenchymatous hepatitis, in which there were large fat droplets with slight or no vitamin A fluorescence.

Lipofuscin.—Lipofuscin was represented by angular lumps of "wear and tear" pigment, located in the center of the cell; it imparted a red fluorescence which was visible after the fading of the vitamin A fluorescence. It was found, with and without vitamin A fluorescence, in various amounts in the liver cells and also in the Kupffer cells. No relation to pathologic change in the liver was noted. However, an increase in lipofuscin was apparent with increasing age.

Jaundice.—The increased bilirubin content was recognized by two phenomena: The cytoplasm of the liver cells imparted a dull green fluorescence, which was not altered by ultraviolet irradiation; and concentrated bile pigments, such as those in the bile casts or in the Kupffer cells in the center of the liver lobules, imparted no fluorescence and stood out as black spots. Such Kupffer cells were free of vitamin A.

In cases of fully developed jaundice the vitamin A fluorescence of the liver as a whole was reduced, the liver cells being poor and the Kupffer cells normal in fluorescence (fig. 2C). This picture was seen in 6 cases in which the icteric index was between 33 and 150 units. In the 3 cases of jaundice in which the icteric index was below 30 units, no reduction of vitamin A fluorescence was seen.

Toxic Edema.—In cases of toxic hepatic edema the interstitial spaces between the liver cell cords and the blood sinusoids are widened and filled with albuminous material. In 5 livers this picture was encountered, localized or evident throughout the lobule (fig. 2B). In the area of edema the liver cells lacked and the Kupffer cells were rich in fluorescence.

Diabetes Mellitus.—In 3 cases of diabetes mellitus a normal or reduced total amount of vitamin A fluorescence was observed. The vitamin A fluorescence of the liver cells was reduced, and that of the Kupffer cells was marked (fig. 2D). In the liver cells the vitamin A fluorescence was imparted by medium-sized fat droplets, which some-

times filled the entire cell. In 2 cases extensive glycogen degeneration of the nuclei⁴ was seen. The cytoplasm in all 3 cases was rich in glycogen despite the extensive fatty infiltration. Apparently vitamin A fluorescence and glycogen may be seen in the same cell.

COMMENT

The study of the biopsy specimens of the liver offers additional evidence for the validity of the histologic demonstration of vitamin A. In animal experiments evidence was obtained for the specificity of the technic. The organs of vitamin A-deficient rats did not show the fluorescence. After the feeding of vitamin A or carotene the fluorescence reappeared in amounts which were in agreement with the doses fed and the chemical assay of the livers for vitamin A. The feeding of no other substance reproduced the fluorescence. This observation was extended to human organs by histochemical comparison of the fluorescence in human and in rat organs. The 2 cases of the present series in which extreme vitamin A fluorescence followed administration of a large dose of vitamin A concentrate offer similar evidence, although it is not as far reaching as that obtained in the animal experiments.

The histologic picture in the biopsy specimens agreed with that in the specimens of liver obtained at autopsy. The distribution of the fluorescence was the same. Some of the observations on the autopsy material^{2b} were substantiated by those made on the biopsy specimens under better controlled conditions and without the complication of the agonal processes, namely, the reduced vitamin A fluorescence and the discrepancy between the amount of fluorescence in the Kupffer cells and that in the liver cells in cases of hepatic damage. This picture has been explained on the basis of inability of the epithelial cells either to hold vitamin A (with subsequent loss to the Kupffer cells) or to remove it from the Kupffer cells. Such a Kupffer cell-liver cell block was present in six cases of jaundice with hepatic damage, in 2 of uncomplicated toxic edema, in 1 of parenchymatous hepatitis, in 1 of cirrhosis and in 3 of diabetes mellitus. The block may be due to damage of liver cells; the presence of bilirubin may interfere with the storage of vitamin A; such interference is seen in the Kupffer cells which show an accumulation of bilirubin.

Clinical vitamin A deficiency in cases of diabetes mellitus has been reported⁵ and explained on the basis of an inability of the liver to con-

4. Rosenberg, O.: Histologische Untersuchungen über das Leberglykogen, *Beitr. z. path. Anat. u. z. allg. Path.* 49:284-312, 1911.

5. Brazer, J. G., and Curtis, A. C.: Vitamin A Deficiency in Diabetes Mellitus, *Arch. Int. Med.* 65:90-105 (Jan.) 1940.

vert carotene to vitamin A.⁶ The high glycogen content of the diabetic liver⁷ cannot be responsible for this condition, since glycogen does not interfere with the storage of vitamin A in liver cells.

An absence of vitamin A fluorescence from the Kupffer cells can possibly be laid to a lack of food intake, since, according to the results of animal experiments, the Kupffer cells are the transfer station in vitamin A metabolism.

Our results suggest that the functional state of the liver cells determines the vitamin A content of the liver. In all cases in which pathologic change of the intralobular parenchyma of the liver was present, the vitamin A fluorescence of the liver cells was markedly reduced; and in nearly all cases in which the amount of vitamin A fluorescence was small, damage of liver cells was present. Pathologic changes in the periportal fields did not exert a decisive influence on the distribution of vitamin A. The low vitamin A content of the body in cases of hepatic disease was shown by chemical assay of the liver,⁸ by the low level of vitamin A in the blood⁹ and by ophthalmologic examination.¹⁰ It was assumed that various causes^{2b} were responsible for the reduced vitamin A content of the liver in cases of hepatic damage. In cases of localized hepatic damage the liver cells failed to show vitamin A fluorescence, in contrast to its presence in the intact areas. This indicated that not only impaired absorption of vitamin A from the intestinal tract, such as was shown by Breese and McCoord,¹¹ but the hepatic damage as such is responsible for the low vitamin A content of the damaged liver.

No definite influence of the nutritional condition or of the pre-operative intake of vitamin A with the food was apparent, except for such extreme conditions as prolonged starvation or large doses of vitamin A concentrate before operation. Moderate emaciation or lack

6. Ralli, E. P.; Pariente, A. C.; Brandaleone, H., and Davidson, S.: Effect of Carotene and Vitamin A on Patients with Diabetes Mellitus: The Effect of Daily Administration of Carotene on the Blood Carotene of Normal and Diabetic Individuals, *J. A. M. A.* **106**:1975-1978 (June 6) 1936.

7. Popper, H., and Wozasek, O.: Zur Kenntnis des Glykogengehaltes der Leichenleber, *Virchows Arch. f. path. Anat.* **279**:819-868, 1931.

8. Moore, T.: The Vitamin A Reserve of the Adult Human Being in Health and Disease, *Biochem. J.* **31**:155-164, 1937. Breusch, F., and Scalabrino, R.: Die quantitativen Verhältnisse der Leberlipide, *Ztschr. f. d. ges. exper. Med.* **94**:569-578, 1934.

9. Lasch, F.: Ueber den Vitamin-A-Spiegel im Blute bei Leberkrankheiten, *Klin. Wchnschr.* **17**:1107-1108, 1938.

10. Rissel, E.: Ueber Vitamin-A-Bildung bei Leberkrankheiten, *Wien. klin. Wchnschr.* **52**:214-218, 1939. Patek, A. J., Jr., and Haig, C.: The Occurrence of Abnormal Dark Adaptation and Its Relation to Vitamin A Metabolism in Patients with Cirrhosis of the Liver, *J. Clin. Investigation* **18**:609-616, 1939.

11. Breese, B. B., Jr., and McCoord, A. B.: Vitamin A Absorption in Catarrhal Jaundice, *J. Pediat.* **16**:139-145, 1940.

of food shortly before operation had no influence. This demonstrates that, with the exception of extremes, the vitamin A content of the liver is more influenced by the functional state of the organ than by nutrition. This is explained by the high storage of vitamin A in normal adults in comparison with the requirements. Many months on a vitamin A-deficient diet are required to deplete adult animals of vitamin A, and the same holds for adult human beings, according to adaptometric studies.

Since the vitamin A fluorescence may be an indication of the functional state of the liver, the fluorescence microscopic examination may be of help in the morphologic analysis of the liver, and the results of such an examination may represent a more sensitive morphologic criterion for hepatic damage than those of the routine histologic examination.

The liver is the most important vitamin A depot of the body; it stores about 95 per cent of the total of vitamin A.¹² The vitamin A fluorescence of the liver may thus indicate the vitamin A requirements of the organism. Our results suggest the importance of administration of vitamin A in cases of hepatic damage.

We intend to continue these studies and to compare the vitamin A stores of the body as determined by the vitamin A content of the liver with that determined on the basis of the level of vitamin A in the blood and on the basis of adaptometric readings in order to evaluate the clinical methods.

SUMMARY

The distribution of vitamin A in specimens of the liver taken for biopsy has been studied by means of fluorescence microscopy. The results substantiated those obtained from study of autopsy material. After intake of a large dose of vitamin A concentrate the fluorescence was strikingly increased. Otherwise, except for prolonged starvation, no striking influence of the nutritional state or the immediate pre-operative intake of vitamin A on the vitamin A fluorescence of the liver has been observed.

Damage of liver cells leads to a reduction of the fluorescence, thus demonstrating the prevalence of the functional over the nutritional factors. A block in the exchange of vitamin A between the Kupffer and the liver cells has been found in cases of liver cell damage, jaundice, toxic edema and diabetes mellitus.

The fluorescence microscopic examination of the liver for vitamin A may help in the morphologic demonstration of damage of liver cells.

12. Sherman, A. C., and Boynton, L. C.: Quantitative Experiments upon the Occurrence and Distribution of Vitamin A in the Body, and the Influence of the Food, *J. Am. Chem. Soc.* **47**:1646-1657, 1925. Moore, T.: Vitamin A and Carotene: The Distribution of Vitamin A and Carotene in the Body of the Rat, *Biochem. J.* **25**:275-286, 1931.

HYPERTHYROIDISM AND ADENOCARCINOMA OF THE THYROID GLAND

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The repercussions of malignant disease on the function of the organ involved are vaguely understood. The effects on organs which secrete hormones are varied, but it is not beyond reason to assume that a malignant lesion originating in an endocrine gland can possess some of the same secretory properties as the benign epithelial tissue from which it derives. The thyroid gland may be the site of such a lesion. It has long been established that the active tissue in the thyroid gland is the epithelium, and frequently evidences of hyperthyroidism are reflected by morphologic changes in the thyroid epithelial cell. It is conceivable that the activity of the thyroid may be altered by the development within the gland of a malignant epithelial tumor or an adenocarcinoma. Because an accurate laboratory test exists to measure the activity of the thyroid gland, it is an ideal organ with which to evaluate the alterations in function accompanying primary adenocarcinoma. The association of hyperthyroidism, or hyperactivity of the thyroid, with primary adenocarcinoma of the thyroid gland is the subject of this essay. As will be seen, the factors involved and influencing this association include not only clinical variations but the coincident presence of other benign pathologic changes in the thyroid gland.

Conflicting reports are available concerning the association of carcinoma of the thyroid gland with hyperthyroidism and with exophthalmic goiter. Joll¹ and Simpson² have reported cases of carcinoma of the thyroid gland associated with hyperthyroidism. Crile³ and Means,⁴ however, have stated that in their experience the two diseases

Portion of a thesis submitted to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

1. Joll, C. A.: *Diseases of the Thyroid Gland with Special Reference to Thyrotoxicosis*, St. Louis, C. V. Mosby Company, 1932.
2. Simpson, W. M.: *A Clinical and Pathological Study of Fifty-Five Malignant Neoplasms of the Thyroid Gland*, *Ann. Clin. Med.* 4:643-667 (Feb.) 1926.
3. Crile, G., Jr.: *Hyperthyroidism Associated with Malignant Tumors of the Thyroid Gland*, *Surg., Gynec. & Obst.* 62:995-999 (June) 1936.
4. Means, J. H.: *The Thyroid and Its Diseases*, Philadelphia, J. B. Lippincott Company, 1937.

do not occur together. In an extensive article published in 1902, Ehrhardt⁵ reviewed the literature on malignant lesions of the thyroid gland. He collected 5 cases of exophthalmic goiter associated with carcinoma of the thyroid gland and added 1 of his own. With the advent of tests for basal metabolism the diagnosis of hyperthyroidism has undoubtedly become more accurate. Elevation of the basal metabolic rate occurs in the presence of adenomatous goiter with hyperthyroidism and of exophthalmic goiter. In both conditions the performance of the accurate laboratory test available for measuring this rate is of diagnostic importance. Thus the determination of the basal metabolic rate in association with careful evaluation of clinical manifestations is likely to lead to a correct diagnosis in the majority of cases. With these factors in mind, a clinical pathologic study was undertaken in an effort to determine the relation of adenocarcinoma of the thyroid gland to hyperthyroidism.

MATERIAL STUDIED

In the cases studied a diagnosis of hyperthyroidism or of exophthalmic goiter was regularly corroborated by determination of the basal metabolic rate, beginning in the year 1917. This does not mean that a determination of the basal metabolic rate was made in every case of carcinoma of the thyroid, for it was obviously unimportant in cases in which there were no clinical signs of thyroid metabolic disturbances. From 1917 through 1937 there were at the Mayo Clinic 412 histologically proved and graded (Broders' method) adenocarcinomas of the thyroid gland. Only primary malignant neoplasms of epithelial origin were considered in this study. Each of the tumors was considered an adenocarcinoma, despite morphologic variations, such as scirrhus, papillary or malignant adenoma. Squamous cell epithelioma, despite the possibility that it arose from thyroid epithelium, was not included, since it was regarded as a metaplastic tumor. No significant change in function was noted in association with squamous cell epithelioma. Proliferating adenoma was not regarded as a separate entity but was classified as adenocarcinoma in an adenoma.

HYPERTHYROIDISM

Incidence.—A clinical diagnosis of hyperthyroidism was made in 57, or 13.8 per cent, of the 412 cases in which adenocarcinoma of the thyroid gland was found. All of the patients underwent operation, and all histologic studies were made on specimens obtained at operation. The frequency of occurrence of various typical symptoms of hyperthyroidism in these 57 cases is listed in table 1. Fixation of the vocal cords is

5. Ehrhardt, O.: Zur Anatomie und Klinik der Struma maligna, Beitr. z. klin. Chir. 35:343-464, 1902.

listed merely to demonstrate how infrequently it occurred in these cases. This relative absence of fixation of the vocal cords indicates that tracheal structures were not infiltrated by the adenocarcinoma and that, as a result, the increased basal metabolic rate was due to metabolic increase in oxygen consumption rather than to mechanical obstruction as Branovacky-Pelech⁶ suggested. Mechanical obstruction was not present in any case to cause dyspnea. In each of the 2 cases in which fixation of a vocal cord was found, only one cord was fixed, and in both the patients presented ample clinical evidence of hyperthyroidism. Chart 1 is the distribution polygon of the basal metabolic rates in the 57 cases of adenocarcinoma of the thyroid gland associated with hyperthyroidism.

TABLE 1.—Incidence of Clinical Phenomena of Hyperthyroidism in Association with Adenocarcinoma of the Thyroid

Clinical Manifestation	Cases
Nervousness.....	57
Palpitation.....	54
Loss of strength.....	53
Dyspnea.....	51
Tachycardia.....	50
Loss of weight.....	49
Tremor of extremities.....	47
Weakness of quadriceps muscle.....	42
Excessive sweating.....	20
Insomnia.....	20
Cardiac enlargement.....	21
Thrill or bruit.....	16
Edema.....	14
Headaches.....	14
Prominent eyes.....	14
Eye signs.....	10
Cardiac irregularity.....	10
Exophthalmos.....	9
Ocular pain.....	8
Vomiting.....	8
Diarrhea.....	8
Fixation of vocal cord.....	2

The lowest rate in this series of cases was + 8 per cent, and the patient presented definite clinical evidence to warrant a diagnosis of adenomatous goiter with hyperthyroidism.

Age and Sex.—Division of the patients with adenocarcinoma and hyperthyroidism into age groups revealed the following facts: The greatest number of patients was in the fifth decade of life at the time of operation. The average age in the entire series of 412 cases was 46.4 years, and in the 57 cases of hyperthyroidism it was 49.4 years. This seeming discrepancy is readily explained by the absence in the first two decades of life of hyperthyroidism associated with adenocarcinoma of the thyroid gland. When the figures are corrected for this factor the average age is about the same. The percentage of each age group in

6. Branovacky-Pelech: Ueber den funktionellen Wert der Langhanschen wuchernden Struma, Mitt. a. d. Grenzgeb. d. Med. u. Chir. 39:609-625, 1926.

which hyperthyroidism was associated with adenocarcinoma began at about 10 per cent in the third decade and rose to about 20 per cent in the seventh decade (table 2).

The evidence of hyperthyroidism was twice as great among women as among men.

Grade of Adenocarcinoma.—The greatest single key factor in the correlation of the pathologic characteristics of the lesion with the clinical symptoms seemed to be the grade of malignancy of the adenocarcinoma. A definite distribution by grade of malignancy was noted in the 57

TABLE 2.—*Age Distribution in Four Hundred and Twelve Cases of Adenocarcinoma of the Thyroid*

Age, Years	Total Patients	Without Hyperthyroidism		With Hyperthyroidism	
		Patients	Per Cent	Patients	Per Cent
0-9.....	6	6	100.0	0	0.0
10-19.....	10	10	100.0	0	0.0
20-29.....	36	32	88.9	4	11.1
30-39.....	85	76	89.4	9	10.6
40-49.....	97	83	85.6	14	14.4
50-59.....	88	74	84.1	14	15.9
60-69.....	73	59	80.8	14	19.2
70-79.....	17	15	88.2	2	11.8
Average age.....	46.4	45.9		49.4	

TABLE 3.—*Distribution of Adenocarcinomas of the Thyroid by Grade of Malignancy*

Grade	Cases	Associated Hyperthyroidism	
		Cases	Per Cent
1.....	125	22	17.6
2.....	156	24	15.4
3.....	60	7	11.7
4.....	71	4	5.6

cases of adenocarcinoma of the thyroid associated with hyperthyroidism. According to Broders' method of grading, the adenocarcinomas, regardless of their morphologic structure, were divided into four grades. Grade 1 represents the least malignant group and grade 4 the most malignant group. The distribution of the 412 adenocarcinomas of the thyroid according to grade of malignancy and the percentage of adenocarcinomas of each grade associated with definite clinical hyperthyroidism are given in table 3.

Represented graphically (chart 2), the relation of the grade of the adenocarcinoma to the frequency of the hyperthyroidism is striking. Hyperthyroidism is much more frequently associated with the lower than with the higher grades of malignancy. Because the grade of the adenocarcinoma is a measure of its anaplasia, or of its degree of

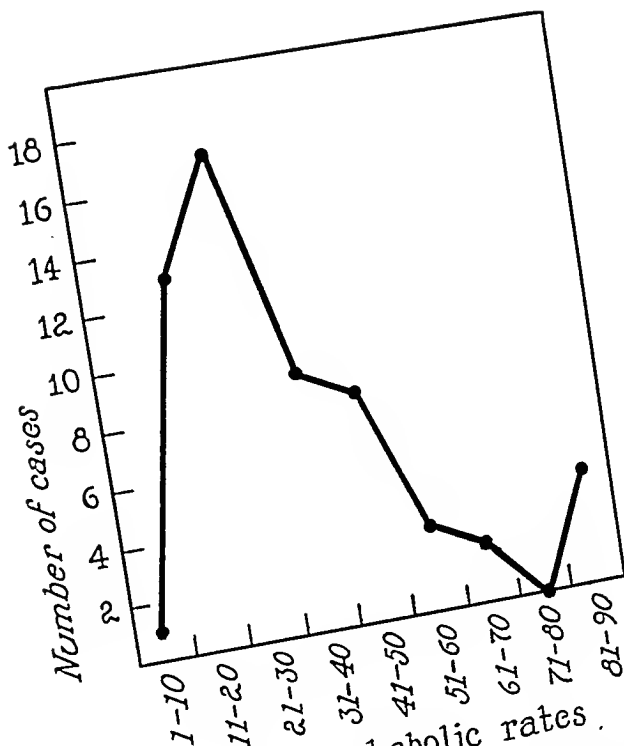


Chart 1.—Distribution of polygon of basal metabolic rates (plus per cent) in 57 cases of adenocarcinoma of the thyroid associated with hyperthyroidism.

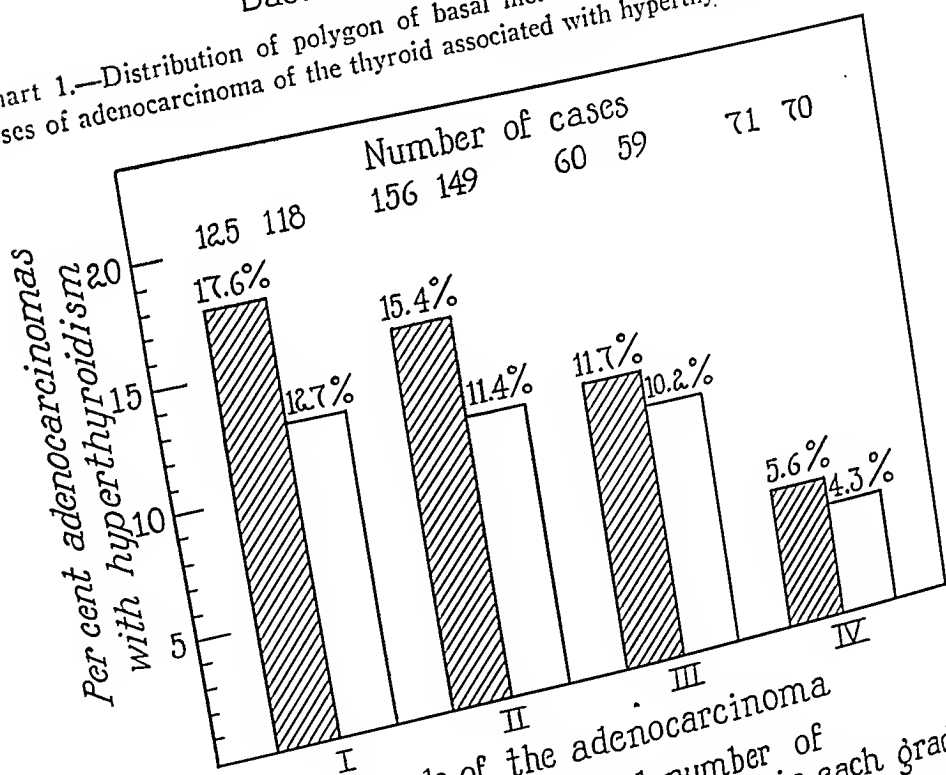


Chart 2.—Relation of adenocarcinoma of the thyroid to hyperthyroidism according to grade of malignancy.

■ Represents % of total number of adenocarcinomas of thyroid in each grade associated with hyperthyroidism.
 □ Same after deducting those cases with parenchymatous hyperplasia (including diffuse and intra-adenomatous varieties).

malignancy, the inference may be drawn that for some reason the more malignant the tumor the less likely is it to be associated with any excess functional activity of the thyroid. The less malignant the tumor the more likely is hyperthyroidism to be associated with it; it cannot be said, however, that the more malignant the tumor the more likely is there to be a decrease in function of the thyroid. Myxedema in association with carcinoma of the thyroid gland, at least in cases in which treatment has not been given, is rare. There have been only 2 such cases at the clinic, and in both of these evidence of cretinism seemed to be present.

A morphologic distinction can be made for the papillary type of adenocarcinoma. The papillary adenocarcinomas in the series were of grades 1 and 2 except for 1 of the mixed type, which was graded 3. If the lower grades of adenocarcinoma are divided into a papillary and a non-papillary type, a similar relation exists between the grade of malignancy and the frequency of associated hyperthyroidism (table 4).

TABLE 4.—*Distribution of Papillary and Nonpapillary Adenocarcinomas and of All Types of Adenocarcinoma of the Thyroid by Grade of Malignancy*

Type of Adenocarcinoma	Grade	Cases	Associated Hyperthyroidism	
			Cases	Per Cent
Papillary.....	1	53	11	13.3
	2	44	1	2.3
Nonpapillary.....	1	42	11	26.2
	2	112	23	20.5
All types.....	1-2	251	46	16.3
	3-4	131	11	8.4

With either type the increase in malignancy is associated with a decrease in the frequency of associated hyperthyroidism. The papillary type, although predominant in the lower grade, is not as frequently associated with hyperthyroidism as is the nonpapillary type.

If grade 1 is combined with grade 2 and grade 3 with grade 4, hyperthyroidism is found to be associated about twice as frequently with the lower grades of adenocarcinoma of the thyroid as it is with the higher (table 4).

Influence of Other Pathologic Features.—Other pathologic features in the thyroid gland must be considered as strongly modifying any hasty opinion which seems to derive inevitably from the foregoing implied relation between adenocarcinoma of the thyroid and hyperthyroidism. The benign gross and microscopic pathologic changes are significantly involved with functional variations of the thyroid gland. The presence of multiple adenomas in the thyroid gland frequently is associated with hyperthyroidism and gives rise to the well established syndrome of adenomatous goiter with hyperthyroidism. For this reason

it was deemed necessary to correlate with the grade of malignancy and hyperthyroidism the gross pathologic changes in the thyroid gland. The 412 cases of adenocarcinoma of the thyroid were divided into four groups according to pathologic changes found, as follows: those in which single nodules or adenomas were present; those in which multiple adenomas were present; those in which the carcinoma was so diffuse as to render the gland a homogeneous mass, and those in which no determination was possible because no operation other than removal of a biopsy specimen was performed. These groups were further subdivided according to grade of malignancy and according to whether clinical hyperthyroidism was present. The results of this reclassification are summarized in table 5.

TABLE 5.—*Frequency of Various Gross Pathologic Changes, Grade of Malignancy and Hyperthyroidism in Cases of Adenocarcinoma of the Thyroid Gland*

Grade	Hyper- thyroidism	Single Adenoma	Multiple Adenoma	No Adenoma (Diffuse Adenocar- cinoma)	Biopsy (No Deter- mination Possible)	Total Cases
1	Absent	25	31	31	16	125
	Present	5	14	2	1	
	Total	30	45	33	17	
2	Absent	31	29	41	31	156
	Present	4	14	6	0	
	Total	35	43	47	31	
3	Absent	13	9	13	18	60
	Present	1	3	3	0	
	Total	14	12	16	18	
4	Absent	4	7	18	38	71
	Present	0	2	1	1	
	Total	4	9	19	39	
Grand total.....		83	109	115	105	412

When the relation of the gross changes was correlated with the absence or presence of hyperthyroidism, certain factors at once became evident. Hyperthyroidism was rarely associated with those adenocarcinomas for which only removal of a biopsy specimen was done. This may be due in part to the fact that less resection was attempted because of the absence of toxic symptoms. In most instances, however, a biopsy specimen was taken because the lesion could not be excised. Biopsy specimens were taken of only 13.6 per cent of the lesions of grade 1, but they were taken of 30 per cent of tumors of grade 3 and of 54.9 per cent of tumors of grade 4. In the 57 cases of hyperthyroidism biopsy specimens were taken in only 2, resection being carried out in all the others. Diffuse adenocarcinoma was present in 12 of these 57 cases (21.1 per cent), and it was impossible to note any adenomas in the glands.

Hyperthyroidism was present in 33 cases in which the thyroid gland contained multiple adenomas in addition to the adenocarcinoma. This is 57.9 per cent of all cases of adenocarcinoma of the thyroid gland associated with hyperthyroidism. The frequency of this occurrence indicates that some relation exists between hyperthyroidism and the presence of multiple adenomas. This observation is not surprising, since adenomatous goiter associated with hyperthyroidism is well established as a clinical and pathologic entity. The exact source of the hyperthyroidism in these cases has not been determined.

The significance of the presence of multiple adenomas in relation to adenocarcinoma of the thyroid associated with hyperthyroidism is at once realized from table 6. Two features may be noted in this table. The first is that the percentage of multiple adenomas associated with adenocarcinoma of the thyroid gland fell markedly with each grade as the grade of malignancy increased. The second is that in about half

TABLE 6.—*Adenocarcinoma of the Thyroid: Percentage of Cases of Multiple Adenomas in Total Group and in Cases of Hyperthyroidism*

Grade	Total Cases	Multiple Adenomas		Hyperthyroidism		
		Cases	Per Cent	Cases	Associated Multiple Adenomas	
					Cases	Per Cent
1	125	45	36.0	22	14	63.6
2	156	43	27.6	24	14	58.3
3	60	12	20.0	7	3	42.9
4	71	9	12.7	4	2	50.0

of the cases in which adenocarcinoma of any grade was associated with hyperthyroidism multiple adenomas were present in the thyroid gland. This does not mean that half the carcinomatous glands which contained multiple adenomas were also associated with hyperthyroidism.

In 24 cases multiple adenomas were not found and hyperthyroidism was present. The explanation of the source of hyperthyroidism in this group is most difficult to find, because the absence of multiple adenomas removes from the field of speculation the most obvious source.

In 83 (20.1 per cent) of the 412 cases studied the thyroid gland contained only a single nodule or adenoma. In 10 (17.5 per cent) of the 57 cases of hyperthyroidism a single adenoma was present in the thyroid gland. Apparently the presence of a single adenoma had no definite relation to the hyperthyroidism, since the percentage of cases of single adenoma associated with hyperthyroidism was slightly less than the percentage of cases of single adenoma in the 412 cases. The 10 glands in the aforementioned cases were studied in more detail in the hope that a clue to the relation to hyperthyroidism might be obtained.

The advantage with this group was that the rest of the gland could be considered as more or less eliminated from consideration of gross pathologic change. In 9 of the 10 glands the carcinoma was confined to the adenoma. In 1 other a diffuse papillary adenocarcinoma was found to be arising in or from a hypertrophic thyroid parenchyma.

In 8 of these 10 glands there was not visible any hypertrophy of the parenchyma to account for the symptoms of hyperthyroidism. The elimination of the factor of multiple adenomas in these glands in which adenocarcinomas were found and in which hyperthyroidism was an associated condition narrows the possible sources of hyperthyroidism to the malignant adenoma. The possibility that the adenocarcinomatous cells were in themselves the source of the hypersecretion and the hyperthyroidism is raised again.

TABLE 7.—*Type of Benign Parenchyma in Cases of Adenocarcinoma Associated with Hyperthyroidism*

	Cases
Multiple adenomas	33
Parenchymatous hypertrophy	11
Colloid parenchyma	22
Single adenomas	10
Parenchymatous hypertrophy	2
Colloid parenchyma	8
No adenomas and colloid goiter.....	5
No adenomas and parenchymatous hypertrophy.....	3
No evidence of any benign tissue.....	4
Biopsies	2
Total.....	57

Except in 2 cases in which operation was done only for removal of a biopsy specimen, the benign tissue of the 57 thyroid glands in which adenocarcinoma was associated with hyperthyroidism was studied histologically. In a few cases evidence of benign tissue could not be found despite the large quantities of tissue removed. As far as could be determined histologically, the parenchyma of the glands was apparently in a state of hyperactivity in 12 cases, and in 4 more cases intra-adenomatous hypertrophy was found. The type of benign parenchyma noted in the 57 cases of adenocarcinoma associated with hyperthyroidism is given in table 7. The apparent absence of any benign tissue in 4 of the 57 glands is an interesting point. Many years ago Carrell-Billard,⁷ Ehrhardt and others noted that despite the absence of any microscopic evidence of benign tissue the function of the thyroid was maintained. Whether

7. Carrell-Billard, cited by Barthels, C.: *Struma maligna*, *Ergebn. d. Chir. u. Orthop.* 24:162-325, 1931.

there is always a small portion of normal thyroid tissue remaining to maintain a normal supply of thyroxin cannot be determined.

The glands containing diffuse parenchymatous hypertrophy can be mentioned only briefly, but I should like to point out that in 7 of the 12 cases multiple adenomas were present.

COMMENT AND SUMMARY

The clinical variations in function known as hyperthyroidism are correlated with the presence of adenocarcinoma in the thyroid gland. The question of whether function and, therefore, hyperfunction can be attributed to adenocarcinoma of the thyroid gland is raised. By analogy, reports of hyperfunction associated with carcinomas of other endocrine organs, if applicable, would settle the question definitely in the affirmative. The infinitely varied and intricate pathologic changes occurring in the thyroid gland preclude such a clearcut conclusion.

TABLE 8.—*Distribution of Adenocarcinomas of the Thyroid by Grade of Malignancy: Cases of Parenchymatous Hyperplasia Omitted*

Grade	Number	Associated Hyperthyroidism	
		Cases	Per Cent
1.....	118	15	12.7
2.....	149	17	11.4
3.....	59	6	10.2
4.....	70	3	4.3

Although a definite conclusion that adenocarcinoma of the thyroid is the source of functional hyperactivity cannot be drawn from this clinical and pathologic study, the evidence points to the possibility that adenocarcinoma of the thyroid, like adenocarcinoma of other endocrine glands, at times and in part may perform the functional role of benign thyroid tissue. The inverse relation between the increase in malignancy and the decrease of frequency of hyperthyroidism seems especially significant. If a correction is made for cases of parenchymatous hypertrophy, because in these the source of the hyperthyroidism appears to be definitely located, then table 8 and chart 2 demonstrate that the fundamental relation between hyperthyroidism and the grade of malignancy still holds.

Only one other feature has been found to have a close connection with the relation of adenocarcinoma to hyperthyroidism, and that is the presence of multiple adenomas. As the grade of malignancy advances, the frequency of occurrence of multiple adenomas decreases, but about half the adenocarcinomas (of any grade) associated with hyperthyroidism occur in thyroid glands containing multiple adenomas. This is not

surprising, because the adenomatous goiter is likely to be associated with hyperthyroidism in a certain percentage of cases.

It is obvious, therefore, that in a majority of cases the benign gross and microscopic changes in the thyroid gland will eliminate quickly the adenocarcinoma as the only possible source of thyrotoxicosis. In some glands no such complicating factors are found. The hypothesis that an anaplastic tumor should retain less of the normal function of its constituent cells as the degree of anaplasia advances is an attractive one and has already been voiced by Ewing.⁸ Some substantiation of this hypothesis may be inferred from this study of 412 histologically proved adenocarcinomas of the thyroid gland. The decrease in frequency of hyperthyroidism with the increasing degree of anaplasia seems to imply such a relation. Function, therefore, may be a property of adenocarcinoma of the thyroid gland and hyperthyroidism an adjunct thereof.

8. Ewing, J.: *Neoplastic Diseases: A Treatise on Tumors*, ed. 3, Philadelphia, W. B. Saunders Company, 1928.

INGUINAL ECTOPIA OF THE OVARY AND FALLOPIAN TUBE

REVIEW OF THE LITERATURE AND REPORT OF THE
CASE OF AN INFANT

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The occurrence in our service of a case of inguinal ectopia of the ovary and fallopian tube prompted us to make a survey of the literature. We have examined the reports to date to determine the incidence of this condition and the outstanding views as to its mechanism of development.

In our review of the literature we found several excellent summaries and compilations of cases. Among them, the reports of Andrews¹ in 1905 and 1906, those of Heineck² in 1912 and 1927 and that of Watson³ in 1923 (revised in 1938) are excellent and complete analyses of reported cases. We decided to bring the compilation to the present, listing the aforementioned data as well as those reported since their publication. We have, however, attempted to restrict our list to cases of inguinal ectopia of the ovary and fallopian tube in an effort to distinguish the condition from simple ovarian and acquired tubo-ovarian hernia. This we found difficult because of the inadequate data given in some reports and the close similarity of these conditions.

We agree with Donald⁴ that if the currently accepted embryologic mechanism is the correct one inguinal ectopia of the ovary, being congenital, is always accompanied with inguinal ectopia of the fallopian tube and is distinct from simple inguinal hernia of the ovary. It must be

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1. Andrews, F. T.: *Tr. Am. Gynec. Soc.* **9**:407, 1906; *Hernia of the Tube Without the Ovary*, *J. A. M. A.* **45**:1625 (Nov. 25) 1905; *Hernia of the Tube and Ovary*, *ibid.* **47**:1707 (Nov. 24) 1906.

2. Heineck, A. P.: (a) *Hernias of Ovary, of the Fallopian Tube, and of the Ovary and Fallopian Tube*, *Surg., Gynec. & Obst.* **15**:63, 1912; (b) *Hernies tubaires, ovariennes, et tubo-ovariennes inguinales et fémorales*, *Union méd. du Canada* **56**:521 and 585; 1927.

3. Watson, L. F.: *Hernia*, ed. 2, St. Louis, C. V. Mosby Company, 1938.

4. Donald, D. C.: *Ectopia and Inguinal Hernia of Ovary*, *Am. J. Surg.* **47**:149, 1940.

admitted that some cases of tubo-ovarian hernia in our list were not instances of true ectopia of the ovary; but it is difficult to separate these in the literature.

ETIOLOGY

As has been pointed out by Donald⁴ and Mauro,⁵ there is a distinct difference between inguinal hernia of the ovary and inguinal ectopia of the ovary. With the former the ovary alone is found lying in the inguinal canal, while with the latter the ovary is accompanied with the fallopian tube. In both instances a persistence of the canal of Nuck and congenitally long ligaments of the ovary and tube play a role in the production of the abnormal position.

Up to this point congenital malformations predispose to both conditions. However, inguinal ovarian hernia is dependent on repeated increases in intra-abdominal pressure, e. g., pregnancies and possibly adhesions of the ovary to herniated mesentery or an intestinal loop (Mauro). This probably accounts for the occurrence of the condition in the older age groups. An associated anomaly of the internal genital organs may or may not be present.

The production of inguinal ectopia of the ovary is dependent on anomalous development of the genital tract. The presence of the ovary and the fallopian tube in the inguinal canal represents a full descent during fetal development and corresponds to descent of the testicle from an intra-abdominal to a scrotal position. Watson³ stated that in his opinion there is not this similarity, "because testicle is retroperitoneal and ovary is intra-abdominal and has a free mesentery."

The mullerian duct and the mesonephric duct are intimately related in the first months of fetal life. Toward the third month the renal and the genital system are well separated and the ovary has reached the false pelvis. The ovary passes into the true pelvic cavity by actual and by relative descent, i. e., the relative differences in growth of the fetal body. Normally, the ovary stops in its descent because of the fixation of the gubernaculum of the ovary, the forerunner of the genito-ovarian (ovarian and round) ligament to the cornu of the uterus. The other end of the gubernaculum of the ovary reaches the base of the labium majus. The canal of Nuck, which extends into the labium majus at this point, usually becomes obliterated at the eighth month of fetal life. If, however, the canal of Nuck remains open, shortening of the distal end of the gubernaculum or the change in the relative growth of the parts, together with failure of attachment of the proximal end of the gubern-

5. Mauro, M.: Contributo allo studio dell'ectopia e dell'ernia inguinale dell'ovaro, Arch. di ostet. e ginec. 41:713, 1934; abstracted, Internat. Abstr. Surg. 60:431, 1935; in Surg., Gynec. & Obst., May 1935.

naculum in time, causes the ovary to be pulled into the canal of Nuck lying within the open inguinal canal. The tube follows the ovary into the canal, since the proximal portion of the mullerian duct is closely associated with the ovary in its development. These features probably account for the evident frequency of inguinal ectopia of the ovary in the infant and for the frequent finding of a firmly adherent ovary and tube within the hernial sac. Of course, adhesions may be present, depending on the length of time the ovary and tube are allowed to remain in this position and subjected to trauma by trusses and pressure bandages. Heineck,^{2b} in his second review of the literature, while distinguishing between acquired and congenital types of tubo-ovarian hernia, concluded that the tubo-ovarian hernia is the final state of tubal and ovarian hernia.

While the conclusions as to the causative factors are based on the known embryologic facts plus anomalies found at operation, additional, less definitely proved, factors undoubtedly play a role in their origin. As was suggested by Donald⁴ and others, a hormonal imbalance occurring at a critical stage in the development of the generative organs may underlie the anomalous results.

It is interesting to note that maldevelopment of the internal genitalia is accompanied at times with anomalous changes in the renal system. Leisching⁶ reported a case of strangulation of the left ovary, tube and broad ligament in the inguinal canal in which at operation the left kidney was found at the brim of the pelvis with its ureter $2\frac{1}{2}$ inches (3.7 cm.) in length. Cullen⁷ reported a case of bilateral inguinal hernia with a tube and an ovary in the right sac, an ovary in the left sac, absence of the left kidney and a right pelvic kidney.

Similarly, ectopia of the ovary is accompanied with additional maldevelopments of the genital tract. Montgomery⁸ pointed out that the tube and ovary found in the sac of a congenital hernia are more common in the presence of a bifid uterus. Shackelford⁹ reported a case of strangulation of the left ovary and tube in the inguinal canal in which there was a bicornuate uterus having a fully developed right cornu and an undeveloped left cornu. There were also two left kidneys, neither of

6. Leisching, A. C.: Strangulated Ovary in and Inguinal Hernia Associated with Congenital Abnormality of Kidney, *Brit. M. J.* **1**:993, 1929.

7. Cullen, T. S.: A Case of Right Pelvic Kidney with Absence of Left Kidney and Ureter, Both Ovaries in Inguinal Canals, *Surg., Gynec. & Obst.* **11**:73, 1910.

8. Montgomery, T. L.: Anomalies of Ovary, in Piersol, G. M.; Bortz, E. L., and others: *Cyclopedia of Medicine*, Philadelphia, F. A. Davis Company, 1934, vol. 9, p. 424.

9. Shackelford, R. T.: Left Urogenital Maldevelopment, *Am. J. Surg.* **35**: 117, 1937.

which was in the renal fossa on that side. Rabinovitz¹⁰ described a bilateral tubo-ovarian inguinal hernia with absence of the uterus and vagina. Shackelford⁹ reported from the records of the Union Memorial Hospital and the Johns Hopkins Hospital 45 cases of incomplete development of the female generative organs. In this list there were 2 cases of left pelvic kidney and 1 case in which an ovary was present in a right inguinal hernia. Shackelford stated that in 8 of 140 cases of tubo-ovarian hernia there were deformities of the genital tract. He also cited Watson as having described 18 cases of bicornuate uterus in 56 cases in which the uterus was found in the sac of an inguinal hernia.

Morse, reviewing Mauro's paper,⁵ stated that the diagnosis of inguinal ectopia should be considered when genital anomalies accompany the tubo-ovarian malposition. He stated that the most important criteria are the presence of a true sac containing the hernia, persistence of the canal of Nuck and genital defects of this canal. The most common are absence or underdevelopment of the uterus, unicornuate or bicornuate uterus and female hermaphroditism. Heineck^{2b} also reported that it is not unusual to see malformations of the uterus, ovary and tube associated with this condition.

From an analysis of the literature it will be seen that further genital defects are not essential criteria for the diagnosis of inguinal ectopia of the ovary. In the great majority of the cases this condition is not associated with additional anomalies.

REPORT OF CASE

At the age of 4 months N. T., a well nourished girl, was treated for a swelling which appeared in the right inguinal region and extended into the labium majus. It was about 2 inches (5 cm.) in diameter, soft, slightly tender and readily reducible.

At the age of 8 months the patient was again seen, because of persistence of swelling in the same area. It had not become any larger, but there was an increase in the difficulty of reduction.

One month later the swelling recurred, becoming increasingly tender, and was associated with vomiting. Attempts to reduce the mass proved futile. Surgical intervention was then planned.

Surgical Procedure.—The patient was prepared for operation and was given a preliminary dose of $\frac{1}{64}$ grain (1 mg.) of morphine sulfate with $\frac{1}{500}$ grain (0.2 mg.) of atropine sulfate. She was then put under ether anesthesia. A Bassini type of incision was made, and the external oblique muscle was incised in the direction of its fibers; the internal oblique muscle was retracted medially, and the canal of Nuck was defined as patent, with a vaginal process of peritoneum extending completely through the canal of Nuck and adherent to the labium by many dense fibrous adhesions.

10. Rabinovitz, M.: Double Ovarian Inguinal Hernia with Absence of Uterus and Vagina, M. Rec. 87:586, 1915.

Dissection was difficult, because of the extremely fragile peritoneum. When it had been accomplished, the opened sac was found to contain the right ovary and fallopian tube. These structures were deeply cyanotic, moderately edematous and attached to the labium by a short gubernaculum of the ovary. When freed, it returned to the normal color promptly and was replaced in the abdominal cavity. The neck of the sac was approximately $\frac{3}{4}$ inch (1.9 cm.) in diameter and had probably contained omentum or a loop of bowel which had reduced itself spontaneously prior to the beginning of the operation. For this reason it was felt that the beginning strangulation of the tube and ovary was due to torsion and not to compression of structures at the neck of the sac. A high ligation of the sac was done with linen at the level of the deep epigastric vessels. The internal oblique muscle was sutured to the inguinal ligament over the canal with single interrupted no. 2 chromic catgut sutures. The remainder of the closure was done in the usual fashion.

Recovery was uneventful, and the patient was discharged in good condition on the eighth postoperative day.

FREQUENCY

In view of the recent distinction between simple inguinal ovarian hernia and inguinal ectopia of the ovary, analysis of past case records and compilations must necessarily lead to some inaccuracies when viewed in this light. While there is little difficulty in recognizing inguinal ectopia of the ovary when it occurs in an infant or a young child it is more difficult to diagnose when it occurs in an older person. When an older person presents a history of evident hernia since childhood, the hernia may be diagnosed as ectopia. So, too, when there is development of an inguinal mass after a strenuous effort or after childbirth without a preceding history of such a disturbance, the condition may be looked on as acquired even though it is evident that some congenital malformation is necessary to its production. Thus, in reanalyzing the literature and presenting the cases as we have done in the table, we have attempted to eliminate the really doubtful cases.

It is worthy of emphasis that the condition we are discussing is not as uncommon as it would seem. It is, we believe, reported infrequently. The diagnosis is not difficult in itself. It is necessary to keep it in mind as a possibility whenever an inguinal mass occurs in an infant girl.

In summing up the total number of cases to date in the world literature, we have examined previous summaries which did not distinguish between the forms of tubo-ovarian hernia which we have described. We have divided the total cases into those in which definite inguinal ectopia of the ovary appeared to be present and those in which there was a questionable element. We have been able to list 138 cases in the former and 57 cases in the latter group. This list includes practically all the cases reported since the latter part of the nineteenth century.

Analytic data on the age of the patient or the actual time when the condition was first noticed fall in line with the conclusion drawn by

Inguinal Ectopia of the Ovary and Fallopian Tube

Author	Age of Patient at Onset	Side Involved	Additional Data	Outcome
1. Andrews ¹ (82 cases up to 1906)	Under 1 year...31 1-2 years.....3 2-5 years.....6 5-10 years.....4 10-20 years.....3 20-40 years.....21 40 years.....7 ?.....7	Cases Right...31 Left...41 Both...5 ?.....5	Cases Strangulation or torsion...16 Other genital anomalies...7 Cystic ovary.....5 Ectopic pregnancy.....4 Ovarian malignant growth...1 Intestine or omentum.....6	Cases Tube and ovary resected...51 Replaced.....20 ?.....7 Autopsy.....3 Death.....7
2. Cullen ⁷	8 years 17 years (5 years previously on left, 3 years later on right)	Left Both	Left kidney and uterus absent; right pelvic kidney	Tube and ovary resected Right ovary and left ovary and tube resected
3. Helneck ³ (41 additional cases to 1912)	Under 1 year...12 1-2 years.....6 2-5 years.....2 5-10 years.....3 10-20 years.....5 20-40 years.....8 40 years.....2 ?.....3 9 cases	Cases Right...14 Left...18 Both...4 ?.....5	Cases Strangulation or torsion...6 Other general anomalies...6 Cystic ovary.....7 Intestine or omentum...3 Uterus in sac.....6	Cases Ovary and tube resected...30 Replaced.....7 ?.....4
4. Coley and Hogue ² (1912), cited by Cohn: New Orleans M. & S. J. 80:723, 1928	Infant 6 months (first noticed at birth)	Right Right	Found in 8,580 hernias of all types at Hospital for Ruptured and Crippled Intestine Torsion of ovary, tube and broad ligament with strangulation None None None	? Replaced Ovary and tube resected Ovary and tube removed Ovary and tube replaced ?
5. Whitecock; Brit. J. Child. Dis. 10:353, 1913.	31 years; present for 5 years	Right	Absence of uterus and vagina	
6. Eastace and McNeely: J. A. M. A. 62:772 (March 7) 1914.	12 years; present for years	Right	None	
7. Daniels: Beitr. z. Geburtsh. u. Gynäk. 18:312, 1913.	2 months 12 weeks; present since birth	Bilateral Right Right	None	
8. Barr: J. A. M. A. 62:451 (Feb. 7) 1914.	5 months Same patient 5 weeks later	Left Right	None	
9. Rathovitz ¹⁰				
10. Hodges: Ann. Surg. 44:958, 1906.				
11. Coff: Brit. M. J. 2:629, 1918.				
12. Muller: Ann. Surg. 67:380, 1918.				

13. Young: New Zealand M. J. 17:91, 1918.....	6 months	Right	Strangulation of tube, ovary and broad ligament	Resected
11. Ludington: New York M. J. 111:956, 1920.....	19 months; present since age of 1 month	Left	Uterus, both ovaries and tubes, broad ligament and knuckle of intestine	All organs replaced
15. Holloperu and Colleville: Bull. Soc. anat. de Paris 17:336, 1920...	2 months	Left	Torsion of pedicle of tube and ovary with strangulation	Ovary and part of tube removed
16. McClannaghan: Tr. Am. Fedlat. Soc. 33:362, 1921.....	2½ months; noticed bilaterally at 5 weeks	Both	Tube and ovary on the left had some strangulation	Tube and ovary replaced on the left
17. Abello, in discussion on McClannaghan.....	3 months	?	Intestine also present	?
18. Summers, in discussion on McClannaghan.....	2 infants	?	?	?
19. Bertaux: Bull. Soc. anat. de Paris 20:761, 1923.....	7 months	Left	Strangulation of ovary and tube; operation under local anesthesia (procaine hydrochloride)	Ovary and tube removed
20. Shumons, cited by Cohn: New Orleans M. & S. J. 80:723, 1928.....	3 years; 1 year duration	Right	None	Replaced
21. Long, cited by Cohn: New Orleans M. & S. J. 80:723, 1928.....	3½ months	Left	Uterus also present	?
22. Harper, cited by Cohn: New Orleans M. & S. J. 80:723, 1928.....	1 to 5 months	?	Strangulation of ovary	?
23. Daggett: Brit. M. J. 2:316, 1925.....	7 weeks	Right	Strangulation of ovary; partial cecit palate	Reduced
24. Dunet and Rousset: Presse méd. 33:100, 1925.....	3 months	Right	Quadruple torsion of pedicle of ovary and tube	Excision
25. Iluquet: Paris chir. 15:298, 1925.....	2 years	Left	Tube and ovary strangulated; inguinal hernia on other side	Resected
26. Rowley: Am. J. Obst. & Gynec. 10:709, 1925.....	81 days; mass at birth	Right	Right and left ovary and tube in sac; ovaries cystic	Replaced
27. Rochet and Peysson: Lyon méd. 136:459, 1925.....	10 months; present at birth	Right	Volvulus of ovary and tube	Ovary and tube removed
28. Touro Infirmary, cited by Cohn: New Orleans M. & S. J. 80:723, 1928	3½ years 35 years 31 years	?	?	?
29. Bruner: Atlantic M. J. 50:280, 1927.....	6 months	Left	Ovary and tube twisted and gangrenous; cornu of uterus in ring	Ovary and tube removed
30. Cohn: New Orleans M. & S. J. 80:723, 1928.....	6 months	Right	Pedicle twisted 5-6 times; round ligament short	Ovary and tube removed; round ligament had to be cut
31. Graffagnino, in discussion on Cohn.....	5 years; present since birth	Left	None	Replaced
32. Leebing: Brit. M. J. 1:923, 1929.....	5 years; present since birth; wore truss for 2 years	Left	Ovary, tube and broad ligament strangulated and gangrenous; left kidney at brim of pelvis; left ureter 2½ inches long; torsion present (tube and broad ligament)	Ovary and tube resected

Inguinal Ectopia of the Ovary and Fallopian Tube--Continued

Author	Age of Patient at Onset	Side Involved	Additional Data	Outcome
33. Wakeley: Surg., Gynce. & Obst. 51: 256, 1930 (period 1916-1929)....	1. 1 year 2 months 2. 4 years 3. 4 years 9 months 4. 1 year 5. 2 months 6. 1 year 4 months 7. 6 months 8. 2 years 9. 2 years 10. 4 years 4 months 11. 9 months 12. 3 years 13. 47 years 14. 7 months 15. 8 years 16. 3 years 5 months 17. 45 years 18. 29 years 19. 53 years	Right Right Left Left Right Right Right Left Right Right Right Right Left Right Left Right Left Left Right	None None None None None None None None None None None None None None None None None None None	Reduced Reduced Reduced Reduced Replaced Replaced Replaced Replaced Replaced Replaced Replaced Replaced Replaced Replaced Replaced Ovary removed Replaced Replaced Ovary removed Ovary removed Replaced Ovary removed Reduced
34. Cepecchi ¹³	21. 1 year 3 months 22. 1 year 1 month 6 months; present at 4 months of age	Right Left Left	None Uterus also present in sac None	Replaced Ovary removed Reduced
35. Mauro ⁵	1. 42 years; duration 8 years 2. 42 years; present since childhood 6 weeks	Left ? Left	Hydroecle and intestine present Omentum present Ovary and tube incarcerated	? ? Reduced
36. Rush and Rush: Am. J. Surg. 29: 140, 1935.....	35 years; present for 12 years	Left	Ovary and tube strangulated; bicornuate uterus; left side undeveloped; atrophic ovary; two left kidneys	Left tube and ovary and uterine cornu excised
37. Shackelford ⁹	41 days	Left	Strangulation of tube and ovary	Tube and ovary removed
38. Vial and Bergeron: Rev. méd. de Nancy 47: 116, 1939.....	26 years, since age of 7 years	Left	Strangulation of ovary, tube, mesovarium and round ligament	Tube, ovary and mesovarium removed
39. Bonah ⁴	8 months	Right	Strangulation of tube and ovary	Reduced
40. Mavor and Templeton.....				

Heineck,^{2a} Watson³ and Wakeley,¹¹ in that the majority, or 64 per cent, of the patients were under 2 years of age and 71 per cent were under 5 years of age. When all the cases were considered, the percentage became 46 per cent under 2, and 50 per cent under 5, years of age. This is not unlikely, in view of the congenital nature of this condition.

Interest in determining whether there is a tendency for this condition to be more prevalent on the left side was stimulated by the opinion held by Bland,¹² who stated that involvement of the left side is much more frequent in cases of inguinal hernia of the ovary. We were not able to conclude that this would hold true for inguinal ectopia of the ovary. We found that among 125 cases in which the pathologic process was taken to be inguinal ectopia and in which the side involved was listed, in 51 (41 per cent) it occurred on the right side; in 61 (49 per cent), on the left, and in 13 (10 per cent), on both. In 14 cases the side involved was not given. Of 57 unconfirmed cases in which the side involved was specified, in 53 per cent the condition occurred on the right and in 47 per cent on the left. In 14 unconfirmed cases the side involved was not stated. These figures lead us to the conclusion that there is no particular predilection for the left side.

In considering the problem of associated anomalies, it was found that of the total 195 patients listed, only 3 had maldevelopments of the renal system; 14 had abnormalities of the genital system, such as bicornuate uterus or absence of the uterus or vagina, and 2 had associated changes occurring in the two systems simultaneously. The cases listed are not likely to include all the possible cases, since in the vast majority exploration of the peritoneal cavity was not possible, the surgical procedure being restricted to the hernial sac and its contents.

From these data one cannot approve the contention of Montgomery⁸ that the condition discussed "is more common in the presence of a bifid uterus."

The most common complication found was torsion or strangulation of the tube or the ovary or both. This occurred in 40 instances. A loop of intestine or omentum was present in the hernial sac in 15 cases. Changes in the ovary, such as cystic degeneration, were noted in 15 cases. Ectopic pregnancy in the ectopic tube occurred 5 times.

The percentage of cures, i. e., those resulting in the preservation of the tube, the ovary or both, is more favorable in the light of more recent reports. The totals taken to date show 56 cases in which the genital organs were saved and 102 instances in which a radical measure,

11. Wakeley, C. P. G.: *Hernia of Ovary and Fallopian Tube: A Record of Twenty-Five Cases*, Surg., Gynec. & Obst. **51**:256, 1930.

12. Bland, P. B., and First, A.: *Displacements of Ovaries*, in Piersol, G. M.; Bortz, E. L., and others: *Cyclopedia of Medicine*, Philadelphia, F. A. Davis Company, 1934, vol. 9, p. 425.

i. e., removal of one or both structures, was required. In 5 cases the organs on one side were resected and those on the other side preserved.

There is no literature available at present to indicate whether the return of the partially damaged ovary and tube is an unwise procedure. The possibilities of cystic degeneration of the ovary and of ectopic (tubal) pregnancy in the damaged structures have been mentioned in support of the radical procedure.

The mortality rate in the reported cases has been very low. No deaths have been reported since the initial compilation of Andrews.¹

DIAGNOSIS

Inguinal ectopia of the ovary is probably more common than the number of reported cases leads one to believe. Its diagnosis may be either simple or difficult, depending on the age of the patient and on the presence or absence of complications.

The diagnosis is made by palpating a firm mass, reducible or not, in the inguinal canal or in the labia. Auscultation reveals no peristaltic sounds. Rectal examination discloses a band (the fallopian tube) stretching from the inguinal ring of the inguinal canal to the cornu of the uterus. Vaginal examination shows displacement of the uterus toward the affected side. Manipulation of the uterus causes movement of the ovary in the canal.

In an infant the labial or inguinal swelling may be present without symptoms. The mass may be readily reducible and nontender, later becoming irreducible and tender. In the former state it must be distinguished from:

1. Inguinal hernia containing bowel or omentum. This is a swelling resonant to percussion and reduced with the characteristic gurgling sound. If it is omentum in the inguinal hernia, these characteristics are not present and the diagnosis is more difficult. There is more apt to be some gastrointestinal disturbance, e. g., constipation, nausea or vomiting.

2. Cyst of the labium majus. This is fixed and not reducible. The rectum and vagina are normal. The mass may be translucent.

3. Cyst of the canal of Nuck. This also is irreducible, translucent and fluctuant.

4. Dermoid cyst of the canal of Nuck. This is irreducible and firm. It may not transmit light.

5. Lipoma. Lipoma is firm, lobulated, asymptomatic, irreducible and opaque to light.

6. Lymphatic enlargement. This may be due to a systemic condition, e. g., lymphatic leukemia, or to a local condition, such as an infection.

In the adult the symptoms are more severe. The ovary in its abnormal position becomes very sensitive. This is accentuated during menstruation. Examinations will reveal a picture similar to that observed in the infant. However, the ovary is less likely to be reducible, because of adhesions to the hernial sac. Vaginal examination reveals a uterus displaced toward the same side as the hernia.

COMPLICATIONS

Like other structures at a foreign site, the ovary and tube are subject to complications. The most common are strangulation and torsion of the pedicle. In addition, there may be cystic degeneration, malignant change in the ovary, salpingitis or tubal ectopic pregnancy. Complicating the picture further, there may be involved with the tube and ovary some other organ, such as the bowel, the mesentery or the uterus.

In the acute phase the following conditions must be considered:

1. Abscess in the labia. This is difficult to distinguish from strangulation of the ovary and tube or torsion of its pedicle, because of marked tenderness and swelling of the adjacent tissues. Rectal and vaginal examination may be of help.

2. Strangulated hernia of the bowel. Watson stated that intestine is present in about 15 per cent of irreducible hernias of the ovary and tube.¹² When both are present the diagnosis is extremely difficult and is dependent on surgical exploration. However, in differentiating strangulated hernia of the bowel from strangulated hernia of the tube and ovary or from torsion of the ovary and tube in the presence of inguinal ectopia the following factors are important:

With the latter conditions (*a*) the general condition of the patient remains good; (*b*) there is no obstruction to the passage of gas; (*c*) on rectal examination the fallopian tube may be palpated passing to the internal inguinal ring, and (*d*) vomiting is reflex, does not have a gastrointestinal origin and subsides in a few days. It never becomes fecal.

3. Inguinal adenitis. The primary site of infection must be looked for. There is a febrile reaction.

TREATMENT

The treatment of inguinal ectopia of the ovary is surgical. It is impossible to determine the number of cases in which the ectopia has been reduced without surgical aid and the reduction permanently maintained. We have found no such cases reported in the literature.

As has been illustrated in several case reports, the hernia and its contents have been retained by means of trusses and pressure bandages for a short time, but these progressed to subsequent strangulation or torsion. Torsion a comparatively frequent complication, particularly in infants.

The surgical procedure is similar to that used for inguinal hernia. The sooner surgical intervention is undertaken, the better the prognosis. The general prognosis remains good at a late stage, even though the symptoms of torsion or strangulation may have persisted for eight to twelve days.¹³

The preservation of the ovary and tube is particularly important, since in the majority of cases the patients are under the age of 2 years. In the preservation of the tube, which may be somewhat damaged, there is the possibility that it may become the site of an ectopic pregnancy during the child-bearing period.

Whenever possible the tube and ovary are returned to the peritoneal cavity and the hernia closed in the usual manner. However, resection of the tube and ovary was found necessary in the majority of the cases reported in Heineck's^{2a} compilation. Of 90 tubo-ovarian hernias, only 14 were reduced. Since that time, in 51 new cases, 31 have been successfully reduced.

The reasons given for resection of the ovary and tube were: (1) complete destruction of the tube and ovary due to torsion and strangulation; (2) malformation of the ovary and tube; (3) ovary and tube being irreducible because of their size; (4) presence of hydrosalpinx or pyosalpinx; (5) atrophic or cystic conditions of the ovary, and (6) neoplasm of the ovary.

For infants, general anesthesia has been found most satisfactory. For adults, spinal and general inhalation anesthetics have been used, depending on preference.

The prognosis is good, and in recent times the mortality has been negligible.

SUMMARY

1. Inguinal ectopia of the ovary is distinguished from inguinal tubo-ovarian hernia.

2. The etiology of this condition is reviewed.

3. A case of true ectopia of the ovary in an infant is presented.

4. A review of 195 cases is reported from the literature.

CONCLUSIONS

1. In the majority of cases inguinal ectopia of the ovary occurs in the first two years of life.

2. There is almost equal distribution as to the side involved.

3. Early surgical intervention with replacement of the organs is the best plan of treatment.

13. Cepecchi, E.: Sullo strozzamento e sulla torsione del peduncolo nelle ectopie tubo-ovariche congenite, Policlinico (sez. chir.) **37**:490, 1930; abstracted. *Int. Surg. Abstr. Surg.* **52**:243, 1931; in *Surg., Gynec. & Obst.*, March 1931.

GYNECOLOGIC MORTALITY

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CLEVELAND

This paper presents a review of the deaths in the gynecologic service from July 1, 1930 to July 1, 1940. A critical study was made of each surgical death in an effort to tabulate factors and faults in the preoperative preparation of the patient, in the operation and in the postoperative course that might have contributed to the fatal result, in order to avoid such mistakes in the future if possible.

Statistics on hysterectomies done in this service have for some years been carefully compiled and reported.¹ Table 1 is a composite table showing the incidence and death rate of this operation for approximately the same period covered by the mortality figures. Hysterectomy of one type or another was done on about 30 per cent of the patients operated on.

The organization of the gynecologic department for these ten years was simple from the surgical standpoint. The personnel of the private service consisted of twelve operators and a radiologist and was a constant group. That of the ward, or staff, service, being organized on the residency system with a senior supervisor, consisted of three operators per year, some of whom were changed at the end of each year. However, no house officer performed a major operation by himself until his fourth or fifth year of hospital training, and then he operated only after a period of supervision.

CLASSIFICATION OF DEATHS

From 1930 to 1940, 147 deaths occurred in the gynecologic service. The general plan of grouping fatalities followed by Marshall and Thompson² was used in this study except that all the records seemed to fall more readily into two main groups than into three. For simplicity it was decided to keep these two groups quite separate in the discussion, with a more detailed analysis of the second group (deaths following elective operations).

From the Department of Obstetrics and Gynecology, the Maternity Hospital, and the Western Reserve University.

1. Faulkner, R. L.: Hysterectomy: A Clinical and Statistical Study, Ohio State M. J. **32**:229 (March) 1936. Weir, W. C.: Statistical Report of 1,914 Cases of Hysterectomy, Am. J. Obst. & Gynec. **42**:285 (Aug.) 1941.

2. Marshall, H. K., and Thompson, R. H.: Mortality Lessons in a Series of 4,029 Gynecologic Operations, California & West. Med. **45**:263 (Sept.) 1936.

Group 1.—This group, of 84 cases, includes instances of death from malignant tumor, death following emergency operation and death from nonsurgical conditions. It is obvious that no detailed analysis need be made. The causes of death are listed in table 2.

To keep the record straight, a brief discussion must be made of some conditions, especially the malignant tumors, the septic abortions, the fatal peritoneal infections and the conditions causing deaths listed as medical.

Malignant Tumor: The vast majority of patients with malignant tumor were admitted just before death, for terminal care only. During this time carcinoma of the cervix was never operated on intentionally. In 2 of the 17 cases total hysterectomy was done under a mistaken diag-

TABLE 1.—Deaths from Hysterectomy (Ten Years)

	1930-1934	Mortality, Per Cent	1935-1939	Mortality Per Cent
Total abdominal hysterectomy.....	821	2.6	1,436	0.77
Subtotal abdominal hysterectomy.....	653	2.3	348	2.3
Vaginal hysterectomy.....	70	2.9	180	3.0

TABLE 2.—Data in Group 1 (Malignant Tumors; Emergency Operations; Nonsurgical Conditions)

Carcinoma of cervix.....	17	Medical causes.....	10
Carcinoma of fundus.....	7	Hemorrhage from tubal preg-	
Carcinoma of ovary.....	14	nancy	1
Septic abortion.....	16	Ruptured gallbladder.....	1
Peritonitis	11	Carcinoma of vulva, bowel,	
Intestinal obstruction.....	3	breasts and bladder, 1 each.	4
Total, 84 cases.			

nosis and a carcinoma was found originating high in the cervix and involving the broad ligaments. One patient died of embolus and the other of shock and hemorrhage. All others were being treated or had been treated with radium and roentgen therapy.

Five patients with malignant tumor of the uterine fundus were admitted for terminal care. The other 2 were operated on; 1 died of embolus, and the other, who had a sarcoma, of hemorrhage and shock.

All carcinomas of the ovary were or had been operated on, at least for exploration and removal of a specimen for biopsy.

Septic Abortion: Treatment of septic abortion, which in the great majority of cases was self induced or criminally induced, was in all but 1 instance conservative. In 1 case the uterus was invaded for what was considered to be serious hemorrhage.

Peritonitis: All patients who died of peritonitis had frank peritonitis, pelvic abscess or a severe pelvic infection on admission to the hospital.

None of them had undergone an operation other than drainage of a localized accumulation of pus (usually by posterior colpotomy) except 1, a pregnant woman in whom peritonitis followed emergency appendectomy at term. At autopsy 2 other pelvic peritoneal infections were observed and were found to have been primarily appendical. The remaining 8 were, as had been thought before death, tubal in origin.

Any death following a pelvic infection for which through an error in diagnosis or judgment the patient was operated on has been included as a death due to an elective surgical procedure.

Nonoperative Deaths: For one reason or another an appreciable number of medical deaths occurred. Some of the patients had not yet come to operation, and some were former patients of the service who were admitted without a clear diagnosis before study in the hospital. The causes of death listed for this subgroup were asthma, terminal tuberculosis of the urinary or the genital tract, toxemia of pregnancy, pulmonary embolus without operation, influenza, septicemia from a pharyngeal infection, cardiac disease (1 case) and granulocytopenia possibly due to sulfanilamide (1 case).

The death by hemorrhage due to an ectopic pregnancy occurred on the elevator en route to the floor. In all cases of intestinal obstruction emergency operations were performed. None of the patients had, at least recently, been operated on in this hospital or elsewhere.

Group 2.—This group, of 63 cases, included all in which death followed an elective operation.

Of the 63 deaths in this group a more critical and detailed analysis was made. The patients, at least before operation, had been expected to get well.

A great many general statistics on average age, height-weight ratios, stay in the hospital before operation, blood counts, etc., are available and could be recorded, but it is thought that inclusion of too many tables, most of which have no bearing, makes for difficult reading; hence only items pertinent to the subject under discussion are included. In general the patients were the ordinary average type observed in a gynecologic service, the great majority being admitted to the hospital when in their late thirties or in the forties.

Especially in the private service, there is not an established practice of holding a patient in the hospital several days before operation unless there is evidence in the preliminary examination to indicate special investigation. No elective surgical operation is ever done on a patient with a hemoglobin level of less than 50 per cent.

The anesthetic used for these patients was (1) nitrogen monoxide, oxygen and ether or (2) avertin with amylene hydrate, nitrogen monoxide, oxygen and ether.

It is desired at once to point out one or two difficulties which were encountered. In some instances there was reasonable doubt of the exact cause of death. This was chiefly true, of course, of a few patients who did not come to autopsy. For example, the impression is gained that the diagnosis of "embolus" is an overworked one. Without autopsy, in 2 or 3 instances, by no reasonable stretch of the imagination could the explanation of death from embolus be sustained. It seemed more likely that in most of these cases (sometimes considerable evidence was obtained from the nurses' notes as well) peritonitis or some other infection was at least the primary cause of death, and this has been recorded. This may slightly exaggerate the number of the deaths from infection and diminish that of the deaths from embolus, but the latter are left as a clearcut group the cause of which was either proved by autopsy or indicated clearly by the manner of death.

TABLE 3.—Data on Group 2 (Death from Elective Operation)

	Autopsy Performed			Autopsy Performed	
Peritonitis.....	22	10	Transfusion	2	2
Hemorrhage and shock....	11	7	Spinal anesthesia.....	1	0
Embolus	10	5	Enteritis	1	1
Pneumonia	5	0	Duodenal fistula.....	1	0
Cardiac disease.....	5	1	Granulocytopenia	1	0
Intestinal obstruction.....	4	2			
Total, 63 cases.					

Another difficulty in some cases, whether autopsy was performed or not, was in selecting a single primary cause of death from all the causes contributing thereto. Perhaps again an occasional arbitrary judgment was passed, due to assigning the most likely cause of death from a surgical point of view obtained after long study of, and consequent familiarity with, the patient's record.

The causes of death among the patients on whom elective operations were performed are listed in table 3.

Peritonitis: Twenty-two patients died of peritonitis. Of these, pan-hysterectomy was performed on 12, supracervical hysterectomy on 4, laparotomy of other types on 5 and a hysterosalpingographic procedure with iodized poppyseed oil on 1. Autopsies were obtained in 10 cases. In several others distinctive symptoms plus positive blood cultures made for a fairly definite diagnosis.

In 2 cases no definite factors contributing to peritonitis were made out. At once, in analyzing contributing causes in the remaining 20, there was encountered some overlapping, i. e., more than one contributing cause was present in some instances.

However, operation done in the presence of a temperature above 38 C. (100.4 F.), a leukocyte count above 8,000 per cubic millimeter or a sedimentation rate below sixty minutes (whether or not explained by the pelvic condition) heads the list of contributory causes. In all cases in which the pelvis was the site of infection pus was spilled. In the 4 cases in which the infection was not in the pelvis there was consistent failure to find out where it was before the operation. In the cases of pelvic infection operation was done through an error in diagnosis or judgment or both. The signs in most cases were thought to arise from degenerated fibroids, twisted cysts or fibroids. Occasional errors in judgment occurred in operations for known pelvic infection, due to inaccurate judgment of the extent or acuteness of the disease and of the condition of the patient. It may be said that in general such operations were done more frequently in the early half of the decade. More and more forcibly there has been driven home the lesson that a rapid sedimentation rate cannot be disregarded.

Difficult operations over two hours in duration or pelvic work combined with operation on the gallbladder or with hernia reduction, which in the final analysis is about the same thing, were next in prominence, contributing to peritonitis in 10 cases. Eight such operations, including the four combined procedures, were not associated with or difficult because of pelvic or other infection. Unusual obesity was present in 3 cases. In 1 case (operation was performed by one of the younger surgeons) insistence on doing panhysterectomy instead of supracervical amputation on a very obese woman who was a poor anesthetic risk probably prolonged the operating time in general. The greater number of deaths from panhysterectomy in this group does not mean that peritonitis is more common after this operation than after other types of hysterectomy. It is the hysterectomy of choice in this clinic, the supracervical procedure being done less often, as may be seen from table 1. It is only fair to say that the subtotal operation is usually performed on the patient who is considered susceptible to infection. This indicates that it is important to study many cases before conclusions are drawn.

Of interest are some of the predisposing causes to peritonitis. In these 22 operations the bladder was torn 3 times, the tear being a definite contribution to infection of the peritoneum in 2 instances. One panhysterectomy was performed (in a case of unsuspected incomplete abortion) in the mistaken belief that the uterus contained a fibroid. Peritonitis followed a hysterosalpingographic procedure done in an outside laboratory in 1 instance. In this series anemia was not a factor, preoperative correction of it when it existed having been thorough. Syphilis was not prominent in these patients, being present in only 2.

The factors contributing to peritonitis may be listed as follows:

Pelvic infection.....	6
Unknown infection.....	4
Long operation.....	6
Combined operation.....	4
Bladder torn.....	3
Incomplete abortion.....	1
Hysterosalpingography.....	1

Therefore, excluding the hysterosalpingographic procedure, twenty-four major factors operated in 20 cases to contribute to peritonitis.

Hemorrhage and Shock: All deaths from hemorrhage and shock occurred within a few hours of operation except 2. In 2 cases reoperation prolonged life to three and eight days, respectively, infection playing a part in the fatal result in both. Autopsy or reoperation confirmed the diagnosis in 9 of the 11 cases. I am of that school whose members believe that fatal shock seldom occurs during a pelvic operation unless there is hemorrhage; therefore, the two conditions are not separated.

Supracervical hysterectomy was performed on 7 of these patients. As in this clinic this type of hysterectomy is performed by most operators only in cases in which trouble is encountered, an idea of why hemorrhage occurred is at once gained. Three of the 7 patients should not have been operated on, as they had preoperative fever, leukocytosis and rapid sedimentation rates from pelvic infection either with or without fibroids. Three of the remaining 4 had large or difficult fibroids, one of which was described as fitting the pelvis like a cork in a bottle. The seventh death occurred by bleeding from a corpus luteum damaged at operation and unnoticed before closure.

Hemorrhage in the remaining 4 cases occurred as follows: (1) in a vaginal hysterectomy done by an occasional operator; (2) in a suspension operation with the point of bleeding never definitely found; (3) in an exploratory laparotomy on a large parasitic fibroid which was never delivered, and (4) in 1 uncomplicated panhysterectomy (the bleeding was postoperative, from the left ovarian pedicle).

In 2 cases failure to correct further an existing anemia could be criticized. Both patients, however, had been given repeated transfusions and were bleeding vaginally. Syphilis was not a prominent factor, being present in but 2 instances.

The factors contributing to hemorrhage and shock may be listed as follows:

Operation for pelvic infection.....	3
Large complicated myoma.....	4
Vaginal hysterectomy by occasional operator.....	1
None except technical.....	3

Embolus: A study of a group of 10 patients who died from embolus yields less information as to contributing factors than does any other group. Embolus is, of course, well known as a complication of pelvic operations as well as an occasional complication of any other operation, even the simplest, and once in a while it occurs without an operation. Pulmonary embolus (including the air embolus) was proved by autopsy in 5 of the 10 cases. In 4 it occurred after panhysterectomy, in 2 after supracervical hysterectomy, in 2 after vaginal hysterectomy and in 1 after a suspension operation. The air embolus occurred during the performance of Rubin's test with an antiquated air apparatus; the patient had small fibroids in the uterus. Curettage had not been done before injection of the air.

In this group there was no preoperative anemia and no positive serologic reaction for syphilis. In only 1 patient was the white blood cell count above 8,000 per cubic millimeter and the sedimentation rate increased; the increase was slight and was not explained by the pelvic condition. Five of the patients underwent operations lasting two hours or slightly more. Prolonged operation was the only more or less constant factor, but none of the procedures were particularly difficult. Therefore, there was no definite contributing cause to embolism in this group. Not routinely, but by most physicians, early activity of the patient is urged, and thyroid medication is used postoperatively to guard against stasis in the circulatory system.

Pneumonia: Five patients who died of pneumonia were anesthetized with nitrogen monoxide, with oxygen and ether or with ether given by the drop method. Three of the operations lasted longer than two hours. None of the patients were above 60 years of age. Two were obese; 2 had positive serologic reactions; 1 was hypertensive, and 1 had a rheumatic heart. The operations included 2 supracervical hysterectomies, 1 vaginal hysterectomy and 1 abdominal panhysterectomy. The deaths were all correlated with the time of year in which the operation was done. None occurred during the winter months, the latest taking place in October. It is perhaps noteworthy that since 1937 no deaths have occurred in the gynecologic service primarily from pneumonia. Perhaps chemotherapy and better general methods of treating this disease, as well as improved anesthetics, have a bearing on this fact. None of the patients had preoperative pulmonary abnormalities; 3 had rapid sedimentation rates not explained by the pelvic condition.

Cardiac Disease: The 5 patients who died of cardiac disease had preoperative diseases in abundance. Three were above 60 years of age. Two who died on being put into the Trendelenburg position were obese and had positive serologic reactions. One was severely diabetic and arteriosclerotic. All died at operation or shortly afterward except 1, who lived twenty-three days, moderate uremia and pelvic peritonitis con-

tributing to the ultimate fatality. Vaginal hysterectomy was performed on 2 of these patients; a mesenteric cyst was excised in 1, and 2 underwent exploratory operations, with subsequent hysterectomy contemplated.

Intestinal Obstruction: Obstruction followed panhysterectomy in 2 instances. One panhysterectomy was a long procedure combined with an operation on the gallbladder; the other was performed on a patient who had a positive serologic reaction for syphilis and an uncorrected low level of hemoglobin (45 per cent [Sahli]) before operation. Obstruction followed supracervical hysterectomy in 1 instance, the patient being a woman 67 years of age. The final patient was a young woman in whom obstruction followed a Baldy-Webster suspension. All were reoperated on except the one in whom obstruction followed the suspension operation. All died on the fifth postoperative day. There have been no primary intestinal obstructions listed as causes of death in the service since 1934. It is possible that some of these patients would have been saved had the Miller-Abbott tube been in use at that time.

Transfusion: There were 2 deaths from transfusion. One of these was due to proved faulty matching and the other was a delayed reaction occurring after three days, the reasons for which were less plain. Permission for autopsy was obtained in both instances.

Spinal Anesthesia: This type of anesthesia is not in common use in our service. One death occurred on the day of operation, after an easy vaginal hysterectomy. It was attributed to bulbar paralysis. Autopsy was not performed.

Enteritis, duodenal fistula and agranulocytopenia, which accounted for 1 death each, are not of statistical value. The patient who died of enteritis had undergone panhysterectomy. The duodenal fistula resulted from operation for an extremely severe pathologic condition of the gallbladder. The granulocytopenia followed an operation for repair only and was thought to be an influenzal type of infection.

Summary of Deaths Following Elective Operations.—Of the 63 cases in which the patients died after an elective operation, peritonitis was the primary cause of death in 30.5 per cent. Death from peritonitis frequently follows operation on a patient with preoperative fever, leucocytosis and particularly a rapid sedimentation rate. Many such patients get well, but some do not, as these figures reveal. Except in rare instances of larger fibroids, a rapid sedimentation rate means accompanying pelvic infection, and immediate operation should no more be done for this combination than for pelvic infection alone. Attention is also called to the occasional rapid sedimentation rate unexplained by the pelvic condition and to the necessity for more preoperative investigation under such circumstances. Peritonitis is apparently more frequent

patients who have been subjected to long or combined operations, even though the operation is not associated with any particular difficulty.

Similarly, death from hemorrhage and shock is frequently associated with operation done in the presence of fever, leukocytosis or a rapid sedimentation rate. In addition, review of the records shows the necessity with large tumors of taking plenty of room and of careful, well organized attack on the blood supply. With the mass ties still considered necessary in pelvic operations, transfixion and double tying of pedicles are indicated, certainly in the hands of the beginner.

No worth while contributory facts as to embolism can be deduced from these cases, but it is pointed out that in half of them the operation, though not difficult, lasted more than two hours.

It is thought that because of improved anesthetics, improved methods of administration of anesthetics and better methods of treating pneumonia this postoperative complication has been less often fatal during the last five years.

In this clinic no deaths from postoperative obstruction were recorded during the last half of the decade under consideration. There is an impression that this complication is becoming less frequent; certainly since the advent of the Miller-Abbott tube it has been less feared.

Syphilis, except in patients with cardiac disease, was not a prominent cause of death from gynecologic procedures.

On the whole, there is no criticism in this clinic of the correction of preoperative anemia.

TREATMENT OF INTUSSUSCEPTION

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During the years from 1920 to 1939, inclusive, 133 patients were admitted to the Children's Memorial Hospital with the diagnosis of intussusception. In every instance the diagnosis was proved either at operation or necropsy, with 15 exceptions, which will be discussed further. Tables 1, 2, 3 and 4 are self explanatory and show some of the pertinent facts concerning the entire group.

Of significance is the fact that enemas given to 64 of the 133 patients failed to produce reduction in all except 11. This is in contrast to Hipsley's¹ results. He procured a reduction in 60 per cent of his patients by this method with only one perforation of the bowel in more than 300 patients. The chief criticism of the method used by Hipsley is that one cannot be certain that reduction of the intussusception has occurred following the enema. Then, too, this method would seem to be useless when the intussusception is above the ileocecal valve.

Various operative procedures were used to produce reduction in the patients whose cases are reported here. In all the patients operated on an attempt was made to procure reduction of the intussusception by the Farr² inflation method and manipulation. In the Farr procedure a rubber catheter with a blood pressure bulb attached is inserted into the rectum before administration of the anesthetic is started. After the abdomen is opened and the intussusception is located, the bowel is inflated through the rectal catheter under the guidance of the operator's hand, and manipulation is started. Inflation alone usually causes a partial reduction and has effected complete reduction in some instances. A reduction by inflation and manipulation was successful for 92 (83 per cent) of the 100 patients on whom the method was employed. When this method failed, other procedures to be described were used. Two patients were operated on by the method which Montgomery and Mussil³ established on an experimental basis. In this operation the unreducible bowel is left in

From the surgical service of Dr. A. H. Montgomery at the Children's Memorial Hospital.

1. Hipsley, R. L.: Intussusception, *J. A. M. A.* **106**:137 (Jan. 11) 1937.

2. Farr, C. E.: A Reduction of Colonic Intussusception by Air Inflation, *Ann. Surg.* **84**:588-590 (Oct.) 1926.

3. Montgomery, A. H., and Mussil, J. J.: The Treatment of Intussusceptions in Children, *Surg., Gynec. & Obst.* **51**:415-419 (Sept.) 1930.

place, and the intussusciens is sutured to the intussusceptum; after this a side to side anastomosis of the bowel is made. One of the 2 patients treated by this method died. In 4 other patients in whom reduction was unsuccessful only a side to side anastomosis was performed, and 3 died. The affected bowel was excised in 4 patients. Three of these had a lateral anastomosis; 1 had an end to end anastomosis, and all died. In 2 patients the bowel was successfully reduced, but its viability was questionable, so a lateral anastomosis was made; 1 lived, and 1 died. One patient on whom a lateral anastomosis was made because of an ulcer of the ileum survived, but another patient who had the same operation for a narrowing of the bowel after Meckel's diverticulum was excised died.

TABLE 1.—*Summary of Results in Cases of Intussusception*

Dates	Patients	Boys	Girls	Average Time in Hospital, Days	Patients Given Preoperative Enema	Cures by Preoperative Enema	Recur-rences After Opera-tion	Deaths
1920 to 1930.....	54	36 (67%)	18 (33%)	7½	29 (54%)	6	None	22 (41%)
1930 to 1940.....	79	51 (61%)	28 (36%)	10½	35 (44%)	5	2 (2.5%)	17 (22%)
Total for 20 years....	133	65%	35%	8.9	64 (48%)	11 (8.3%)	2 (1.5%)	39 (29%)

TABLE 2.—*Ages of Patients in Whom Reduction Was Successful*

Dates	Under 1 Yr.	1 to 2 Yr.	2 to 3 Yr.	3 to 4 Yr.	4 to 5 Yr.	5 to 6 Yr.	6 to 7 Yr.	7 to 8 Yr.	8 to 9 Yr.
1920 to 1930.....	41	6	2	3	0	2	0	0	0
1930 to 1940.....	51	18	5	2	0	0	1	0	2
Total for 20 years	92	24	7	5	0	2	1	0	2

Ileostomy alone was performed on 3 patients, and they died. In 1 patient the intussusciens was incised and the bowel then sutured longitudinally; death followed. Of these 18 patients in whom some operative procedure was performed on the bowel itself, 14 (78 per cent) died.

Spontaneous reduction occurred in 1 patient during operation. In 4, the bowel was found reduced at operation.

Eighteen patients were not operated on. In 11 of these reduction was obtained by an enema, and in 3 reduction was thought to have come about spontaneously. Three died. Operation was prohibited by the parents of 2 patients; 1 of these recovered, and the other died at home.

During the decade from 1920 to 1930 there was a total of 54 patients admitted, with 22 deaths (41 per cent); in the following decade from 1930 to 1940 there were 79 admitted and 17 deaths (22 per cent). This shows the decrease in mortality which results from experience; some of the surgeons were in attendance the entire twenty years.

In 2 recently admitted patients, reduction could not be accomplished by the method of rectal inflation and bowel manipulation. Brief histories of these 2 cases are now presented.

REPORT OF CASES

CASE 1.—A Polish boy aged 4 months was brought to the Children's Memorial Hospital Nov. 11, 1939 with a history of vomiting and bloody stools during the preceding twenty-four hours. The child appeared toxic. A cylindric mass was palpable beneath the left rectus muscle. Rectal examination revealed a cervix-like mass and blood on the examiner's finger. A laparotomy was performed, and an ileocecal intussusception was found extending from the lower part of the ileum to

TABLE 3.—Time of Operation with Reference to Onset of Illness

Dates	Cases	Within First 12 Hr.	12 to 24 Hr.	24 to 48 Hr.	48 to 72 Hr.	Over 72 Hr.
1920 to 1930.....	46	6 (13%)	5 (11%)	10 (22%)	9 (19%)	16 (35%)
1930 to 1940.....	69	19 (27%)	4 (6%)	18 (26%)	13 (19%)	15 (22%)
Total for 20 years.....	115	25 (22%)	9 (8%)	28 (24%)	22 (19%)	31 (27%)

TABLE 4.—Preoperative Findings

Dates	Patients	Patients with Preoperative Vomiting	Patients with Preoperative Abdominal Mass	Patients from Whom Rectal Blood Was Obtained on Examiner's Finger
1920 to 1930.....	54	53 (98%)	38 (70%)	19 (35%)
1930 to 1940.....	79	70 (88%)	58 (73%)	45 (58%)
Total for 20 years.....	133	123 (92%)	96 (72%)	64 (48%)

the lower part of the rectum. Inflation of the bowel through a rectal catheter and manipulation failed to disengage the proximal 2 inches (5 cm.) of the invaginated bowel. About 10 cc. of glycerin was then injected with a syringe between the intussusciens and the intussusceptum. The neck of the intussusciens was grasped to retain the glycerin, and the right forefinger was placed into the neck and moved around to distribute this lubricant. Reduction was thus accomplished, and recovery was uneventful.

CASE 2.—A white boy aged 7 months was admitted March 30, 1940 with a history of vomiting of eighteen hours' duration. A sausage-shaped mass about 3 inches (7.5 cm.) long was palpable in the left side of the abdomen. During rectal examination blood was revealed on the examiner's finger. At laparotomy an ileocecal intussusception about 10 inches (2.5 cm.) long was found that could not be reduced by rectal inflation and manipulation. Glycerin was injected as in the preceding case and reduction accomplished. Recovery was uneventful.

The high mortality rate of this disease relates especially to the group of cases in which reduction is impossible. A method was sought which

would increase the number of cases in which reduction could be obtained by manual methods.

On viewing an intussusception before reduction one might believe that there was a narrow ring at the neck of the intussusciens and that this prevented reduction. After reduction, however, no narrow ring is seen at this site. There is, however, some thickening of the bowel wall, in most instances due to edema. A finger can be introduced into the neck and readily swept from one mesenteric border to the other. Hence, narrowness of the ring does not seem to be the chief cause for the failure of reduction; in many instances the reason seems to be that the bowel serosa is inflamed and roughened. This condition causes the two opposing bowel layers to adhere to one another, with friction, and thus prevents reduction. It was thought probable that a lubricant introduced between the intussusciens and the intussusceptum would obviate this difficulty of reduction. Glycerin was chosen as the substance least likely to damage the bowel. Furthermore, glycerin is hygroscopic and probably has some tendency to remove the edematous fluid from the bowel wall, thereby assisting in reduction.

Glycerin was successfully employed in the aforementioned 2 patients in whom reduction was impossible. Five to 10 cc. of glycerin was injected between the intussusciens and intussusceptum with a 2 cc. syringe. On removal of the syringe the neck was grasped with the thumb and forefinger of the left hand, while the forefinger of the right hand was introduced through the neck and swept the glycerin around from one mesenteric border to the other as further attempts were made at disinvagination. Finally complete reduction was obtained. After reduction was gained, as much as possible of the glycerin was removed with a sponge.

SUMMARY

In the years from 1920 to 1940, 133 patients were admitted to the Children's Memorial Hospital, Chicago, with a diagnosis of intussusception. The mortality rate for those admitted from 1920 to 1930 was 41 per cent; the mortality rate from 1930 to 1940 was 22 per cent. In 2 patients with irreducible intussusceptions glycerin was injected between the intussusciens and the intussusceptum and successful reductions accomplished.

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RELATION OF SPLENIC EXTRACT TO ETIOLOGY OF ESSENTIAL THROMBOPENIA

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In 1938 Troland and Lee¹ reported 3 cases of thrombopenic purpura in which they were able to prepare from the patient's spleen an extract which had platelet-reducing properties when injected into rabbits. In all 3 cases splenectomy resulted in amelioration of symptoms. The spleens were small, the largest weighing 136 Gm. Similar work had been reported by Torrioli and his associates,² beginning in 1933; attempts at confirmation have thus far been inconclusive.³ Following the methods of Troland and Lee, we attempted to confirm their results. Our first extract was prepared from a spleen removed at another institution. We were able to secure three more spleens, one from the surgical service of the Flower and Fifth Avenue hospitals.

METHODS

Extraction.—Splenic tissue was chopped fine and placed in five times its volume of reagent acetone (chemically pure) immediately after removal. The first extract (to be known as extract A, fractions as A-1, etc.) was prepared after six months' ripening; the length of ripening and case histories for extracts B and C are unknown, the spleens from which they were prepared having been sent to us as a control on experiments being done simultaneously at another institution. The period of ripening of extract D-1 was one week after splenectomy; that of extract D-2, two weeks; that of extract D-3, three weeks, and that of extract D-4, three months. Except when otherwise noted, the method of extraction was the same in all instances. Sterile equipment was employed throughout.

A quantity of supernatant acetone was removed with a pipet from the splenic tissue below and filtered into a glass vessel with a side arm through sterile hard

From the Graduate School, Division of Surgery, New York Medical College, Flower and Fifth Avenue Hospitals and the Metropolitan Hospital.

1. Troland, C. E., and Lee, F. C.: Thrombocytopen, J. A. M. A. **111**:221 (July 16) 1938.

2. Torrioli, M., and Puddu, V.: Recent Studies on the Pathogenesis of Werlhof's Disease, J. A. M. A. **111**:1455 (Oct. 15) 1938.

3. Hobson, F. C. G., and Witts, L. J.: Platelet Reducing Extracts of the Spleen, Brit. M. J. **1**:50 (Jan. 13) 1940. Major, R. H., and Weber C. J.: Is There a Platelet Reducing Substance in the Spleen of Thrombocytopenic Purpura? J. Lab. & Clin. Med. **25**:10 (Oct.) 1939.

filter paper. Distillation was carried out by using negative pressure from a water aspirator, the system being air tight. The temperature was kept between 25 and 29 C.

Distillation was discontinued when constant volume was maintained and the residue was orange-brown and syrupy. The residue was then dissolved in sterile distilled water sufficient to equal the predistillation volume and was stored in a vaccine bottle in a refrigerator.

Fraction A-9 was prepared by allowing the acetone to evaporate in open air for twenty-four hours. The residue was treated as usual. Fraction D-3 was prepared by bubbling air through a fine capillary tube placed in the acetone solution; the residue was treated according to routine.

Several fractions were tested qualitatively for acetone by the nitroprusside method; all samples gave a strongly positive reaction. Since acetone was present in all samples tested, it could not account for the low counts obtained for rabbits 1 and 3.

Fraction A-8 was tested by the bacteriology department to check on our technic; no growth in pour plates or in broth cultures was reported.

Standardization.—After observation the apparent effectiveness of our extract in rabbits 1 and 3, we attempted to standardize its potency. We used white mice weighing 6 to 8 Gm. Intraperitoneal injections of as much as 1 cc. were not lethal; the animals were killed after twenty-four hours, and no hemorrhagic phenomena were seen at autopsy.

Animals.—Rabbits weighing 4 to 8 pounds (1.8 to 3.6 Kg.) were used throughout the experiments. From rabbits 5, 6, 9, 10 and 17 biopsy specimens were taken of the femoral and costal marrow and of the spleen. Four to six weeks was allowed for recovery from the effects of operation. Histologic examination of the same tissues at the end of our experiments showed no significant changes. Slides of spleen and bone marrow from rabbits 1 and 3 were also normal.

Sources of Extracts.—The A series of extracts was prepared from a spleen weighing 136 Gm., removed from a 33 year old woman in whose case a diagnosis of essential thrombopenic purpura had been established clinically at another institution. We know nothing about the spleens from which extracts B and C were prepared, these having been sent to us as controls only; they may have been removed for another reason.

The complete history of the patient from whose spleen the D series was prepared is available and is presented in abstract form. E. C., a girl aged 8 years, in 1936 reported to the outpatient department with a history of spontaneous petechiae and ecchymoses beginning at the age of 2 years. At the first visit the platelet count was low and the tourniquet test gave a negative result. During the next four years the patient was seen several times; thrombopenia, with a platelet count of about 100,000 per cubic millimeter of blood, was consistently noted; clot retraction became delayed, and the Hess test gave a positive result. Remissions were noted by the family. At different times hemorrhagic phenomena were found in the skin, conjunctivas, oral mucosa and tympanic membrane. The onset of symptoms often coincided with the onset of an infection of the upper respiratory tract, which was the chief complaint on four admissions to the hospital. In view of the (at times) prolonged bleeding time (up to twenty-one and one-half minutes) and poor clot retraction, tonsillectomy was refused by the department of otolaryngology. In April 1940 she was admitted with widespread purpura and tonsillitis; the latter cleared up under treatment. The platelet count was 30,000

per cubic millimeter; there was no anemia; the bleeding and coagulation times were normal; the Hess test gave a positive result, and the bone marrow was normal except for an increase of megakaryocytes. It was decided that she had chronic recurring essential thrombopenic purpura and that in view of the widespread distribution of the purpura a more serious accident could occur. The platelet count was repeatedly below 50,000 per cubic millimeters; forty-five minutes before operation a count of 45,000 was recorded. On April 14, 1940, splenectomy was performed; the spleen weighed 96 Gm. and was microscopically "compatible with thrombopenic purpura." Immediately after ligation of the pedicle the platelet count was 100,000 per cubic millimeter; in twenty-four hours it was 172,500; daily counts thereafter were 197,500; 320,000; 530,000; 615,000; 560,000; 500,000; 510,000, and, in two weeks, 700,000. After discharge she returned to the clinic on June 26 with a recurrence of the purpura despite a normal platelet level. On October 9 she returned for follow-up examination. The history revealed the occurrence of the menarche, with normal menses in August and September, of average quantity and duration. During July the purpura had cleared up. The platelets numbered 360,000 per cubic millimeters; the bleeding, clotting and clot retraction times were not prolonged, and the Hess test gave a negative result. By November 7, a relapse occurred, many ecchymoses and petechiae being present; the coagulation time was seven and one-half minutes, and the bleeding time, nine minutes; the platelets numbered 20,000 per cubic millimeter, and the tourniquet test gave a positive result. A normal menstrual period was reported for October. On Jan. 22, 1941, E. C. reported for follow-up examination; normal menses were recorded for November, December and January. The petechiae and ecchymoses noted on the previous visit faded shortly thereafter and have not recurred. No time has been lost from school to date, and only one episode of disease of the upper respiratory tract has occurred. Physical examination revealed the girl to be well nourished and well developed. She showed no hemorrhagic phenomena. The tourniquet test gave a negative result; the bleeding time was three minutes and five seconds, and the platelets numbered 180,000 per cubic millimeter. We believe that the evidence to date confirms the clinical diagnosis of essential thrombopenic purpura.

During hospitalization the patient was tested with intracutaneous injections of an extract of her own and of one other spleen (extract A preoperatively). She did not react.

All platelet counts reported in this paper were determined according to the method of Rees and Ecker.⁴ Our technic was checked several times by technicians on the hospital staff.

EXPERIMENTAL STUDIES

After the preinjection level of the blood platelets had been established the extract was injected intravenously into rabbits. As can be seen in the accompanying table, counts were done at varying intervals. An analysis of the results shows that rabbits 1 and 3 gave markedly positive reactions, registering definite and large decrease in the platelet level; the transitory drop was accompanied with an increased bleeding time for rabbit 1 only. It was decided to call the extract potent if the platelet level fell to the neighborhood of the critical level of Duke, 35,000 per cubic millimeter.⁵ In none of the other experiments was there a drop which

4. Rees, H. M., and Ecker, E. E.: Improved Method for Counting Blood Platelets, *J. A. M. A.* 80:621 (March 3) 1923.

5. Duke, W. W.: The Relation of Blood Platelets to Hemorrhagic Disease. *J. A. M. A.* 55:1185 (Oct. 1) 1910.

Data on Experiments with Splenic Extracts

	1	2	3	4	4	4	5	6	7	8	9	10	11	12	13	14	15	16	17
Rabbit.....	415	455	445	670	690	770	410	390	475	465	415	420	535	610	460	550	610	415	530
Preinjection level.....																			
Extract: Number.....	A-1	A-2*	A-3	B	O	A-4	A-5	A-6	A-7	A-7	A-8	A-8	A-8	A-8	A-9	D-1	D-2	D-3	D-4
Amount, cc.....	1.8	1.7	7.5	6	5	3.5	3	6.8	7.5	2.5	2	2	2	2	2	5	8.25	7.8	5
Platelet counts * and time elapsed	53†	350	95	495	505	495	475	610	575	275	490	510	505	615	332	4 hr.	4 hr.	4 hr.	5 hr.
	26 hf.	6 hr.	26 hr.	7 hr.	7 hr.	6 hr.	7 hr.	7 hr.	7 hr.	7 hr.	6 hr.	7 hr.	7 hr.	10 hr.	13 hr.
	240	385	425	325	502	450	435	510	730	415	525	470	560	530	480
								B.T. 9'											
								11 hr.	10 hr.	11 hr.	12 hr.	12 hr.	12 hr.	12 hr.	24 hr.	12 hr.	11 hr.	24 hr.	
								350	367	500	505	475	605	560	380	605	550	605	
								B.T. 1½'											
								24 hr.	24 hr.	24 hr.	24 hr.	24 hr.	24 hr.	24 hr.	24 hr.	24 hr.	2 days	
								425	437	500	375	405	450	550	450	570	450	
								2 days	2 days	2 days	2 days	2 days	2 days	
								530	625	605	505	430	430	
								2 days	Simultaneous determinations	Simultaneous determinations	8 days	
								4 days	Simultaneous determinations	Simultaneous determinations	500	
								6 days	Simultaneous determinations	Simultaneous determinations	17 days	
								4 days	Simultaneous determinations	Simultaneous determinations	490	
								6 days	Simultaneous determinations	Simultaneous determinations	
								7 days	Simultaneous determinations	Simultaneous determinations	
								8 days	Simultaneous determinations	Simultaneous determinations	
								9 days	Simultaneous determinations	Simultaneous determinations	

* Counts in thousands per cubic millimeter.

† Bleeding time 11 minutes; bleeding time determined with each count, and all were in normal range.

‡ Extract frozen and thawed at room temperature.

even approximated this arbitrary standard. In only 1 other instance was the bleeding time increased above normal (rabbit 5, nine minutes); the lowest platelet count in this instance was 325,000.

Rabbits 7 and 8 were used to control the dosage; rabbit 8 (dose, 2.5 cc.) registered a greater drop than rabbit 7 (dose, 7.5 cc.). This decrease still did not approach the level set for potency of the extract. Extract A-8 was injected into 4 rabbits so that simultaneous determinations could be made; these animals showed practically no diminution of platelets.

We are not prepared to speculate on the instance in which elevation of the count was noted. We cannot explain the paradoxically excellent results with rabbits 1 and 3.

SUMMARY

Seventeen experiments were performed with extracts of spleens removed in cases of idiopathic purpura haemorrhagica of Werlhof. Two of these (experiments 1 and 3) gave positive results. The results of the rest were, in our opinion, negative, although in some there were slight transitory drops. In several instances the counts rose rather than dropped. One patient was given a cutaneous test with an extract of her own and one other spleen and was found not to react. In those rabbits in which thrombopenia was produced no spontaneous hemorrhagic phenomena appeared; in only 2 cases was the bleeding time prolonged. Two experiments were done with extracts made from spleens removed for an unknown cause; these extracts likewise showed no potency.

CONCLUSION

We were unable to demonstrate consistently the presence of a platelet-reducing substance in acetone extracts of spleens from patients with thrombopenic purpura of Werlhof or in extracts from 2 spleens of unknown pathologic condition when injected into rabbits.

NERVES IN THE VERTEBRAL CANAL

THEIR RELATION TO THE SYMPATHETIC INNERVATION OF THE UPPER EXTREMITIES

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According to current accounts of the nerves in the vertebral canal, based mainly on the work of von Luschka (1850)¹ and Rüdinger (1863),² a recurrent or meningeal nerve arises from the communicating ramus of every spinal nerve and enters the vertebral canal through the corresponding intervertebral foramen. Within the vertebral canal these nerves bifurcate, sending a short division cephalad and another caudad. These divisions constitute a longitudinal strand of nerve fibers, the sinuvertebral nerve, located in the lateral region of the floor of the canal. Branches arising from the sinuvertebral nerve convey fibers to the meninges, to the blood vessels within the canal and to the membranes enveloping the spinal nerve roots.

Certain clinical observations reported by Simpson, Brown and Adson (1930),³ White (1933),⁴ Telford (1934)⁵ and others support the assumption that in certain cases some sympathetic fibers in the upper extremity remain functionally intact following extirpation of the inferior cervical and upper two or three thoracic segments of the sympathetic trunk, an operation which cannot be carried out without interrupting all known pathways through which sympathetic nerve fibers enter the brachial plexus. The present investigation has been undertaken to determine the distribution of the sympathetic components of the nerves within the vertebral canal more accurately and to test the hypothesis that sympathetic nerve fibers which enter the vertebral canal

From the Department of Microanatomy, St. Louis University.

1. von Luschka, H.: *Die Nerven des menschlichen Wirbelkanales*, Tübingen, H. Laupp, 1850.

2. Rüdinger, N.: *Ueber die Verbreitung des Sympathicus in der animalen Röhre, dem Rückenmark und Gehirn*, Munich, J. J. Lentner, 1863.

3. Simpson, S. L.; Brown, G. E., and Adson, A. W.: *Observations on the Etiological Mechanism in Raynaud's Disease*, *Proc. Staff Meet., Mayo Clin.* **5**:295-298, 1930.

4. White, J. C.: *Progress in Surgery of the Sympathetic Nervous System* in 1932, *New England J. Med.* **209**:843-850, 1933.

5. Telford, E. D.: *Sympathectomy: A Review of One Hundred Operations*, *Lancet* **1**:444-446, 1934.

at lower levels emerge through lower cervical and upper thoracic intervertebral foramens and join the nerves which innervate the upper extremity.

MATERIALS AND METHODS

The material used in the present study was obtained from normal and experimental animals (cats) and a human fetus at full term. The preparations of normal material consisted mainly of transverse sections of the decalcified vertebral column, including the spinal cord and meninges. In a series of normal young cats and a full term human fetus, the vertebral column with the contents of the vertebral canal was dissected out from the level of the eighth cervical to that of the tenth thoracic nerve, fixed in Bodian's ^{5a} solution no. 2, to which 5 Gm. of chloral hydrate per hundred cubic centimeters had been added, and then placed in Schridde's solution long enough to insure complete decalcification of the vertebrae. Paraffin sections of this material were impregnated with strong protein silver and toned with gold chloride.

Cats of another series were subjected to an operation in which the inferior cervical ganglion and the first, second and third thoracic segments of the sympathetic trunk were removed unilaterally and several of the upper thoracic spinal nerves on the same side were sectioned within the vertebral canal. The animals were killed four weeks after the operation. Then the contents of the intervertebral foramens on the side of the operation, through which the eighth cervical and the first and second thoracic nerves emerge, including the tissues connecting the vascular plexuses in the vertebral canal with these nerves, were carefully dissected out and prepared by the pyridine-silver technic. This material was sectioned serially, some of it transversely and some longitudinally.

Cats of a third series were subjected to unilateral extirpation of the inferior cervical and upper six thoracic sympathetic ganglions with the intervening portions of the sympathetic trunk. When these animals were killed, four weeks after the operation, all the segments of the vertebral column affected by the operation were dissected out, with the spinal cord intact, fixed, decalcified, sectioned and stained by the same methods as the material from the other animals.

ANATOMIC FINDINGS

In the sections of the material obtained from the animals not subjected to operation, bundles of nerve fibers arranged longitudinally were observed ventral to the longitudinal vertebral venous sinus and between it and the periosteum of the vertebrae. These bundles comprised both myelinated and unmyelinated fibers, but the unmyelinated always outnumbered the myelinated ones. They occupied approximately symmetric positions in either side of the vertebral canal and were accompanied by arteries. They maintained fairly constant positions between the periosteum and the venous sinuses throughout the length of the portion of the vertebral canal which was included in the serial sections (fig. 1). These nerves gave rise to branches, not all of which contained myelinated fibers. Some of the smaller ones were accom-

^{5a} Bodian, D.: Staining of Paraffin Sections of Nervous Tissues with Activated Protargol: Role of Fixatives, *Anat. Rec.* 69:153-162, 1937.

panied by arteries and eventually entered the bony substance of the vertebrae; others extended outward in the intervertebral foramina in the connective tissue ventral to the spinal nerves. Every spinal nerve in the segments studied was joined by such a branch, which extended dorsalward through the longitudinal vertebral venous sinus and assumed a position in proximity to the more anterior motor rootlets of the spinal nerve which it accompanied outward in the intervertebral foramen (fig. 2). Some branches entered the vertebrae, but none were observed which crossed the medial plane.

Bundles of unmyelinated nerve fibers also were present in the dorsal region of the vertebral canal. They lay between the periosteum of the lamina of the vertebra and the posterior internal vertebral venous plexus.

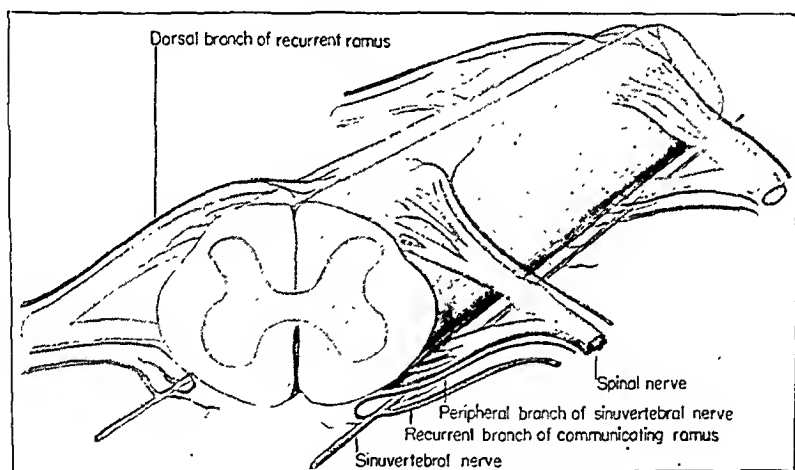


Fig. 1.—Nerves in the vertebral canal.

These bundles were small and did not maintain constant positions throughout the length of the canal. Most of them penetrated the bone of the vertebrae, but some pierced the ligamenta flava and extended outward between the arches of the vertebrae. Others extended into the intervertebral foramina in the connective tissue dorsal to the spinal nerves. Connections between the nerves lying ventral to the longitudinal vertebral venous sinus and those located dorsal to the internal vertebral plexus could not be observed.

In preparations of the material obtained from the human fetus, the arrangement of the recurrent rami and the nerves in the vertebral canal conformed in all essential respects to the pattern observed in the cat, but the nerves were relatively larger. The greater abundance of nerve components in the human vertebral canal is probably correlated with the greater complexity of the blood vessels.

In sections of the material taken from the animals which had been subjected to the operation involving removal of the sympathetic trunk from the inferior cervical to the seventh thoracic ganglion, the nerves lying ventral to the longitudinal vertebral venous sinus were present throughout the segments in question on the side on which operation had been performed as well as on the other. In the upper segments most of the smaller bundles of fibers had undergone degeneration on the operative side. Only the larger bundle persisted and some of its constituent fibers had degenerated. Some intact fibers deviated from this nerve and extended outward in the intervertebral foramens, close

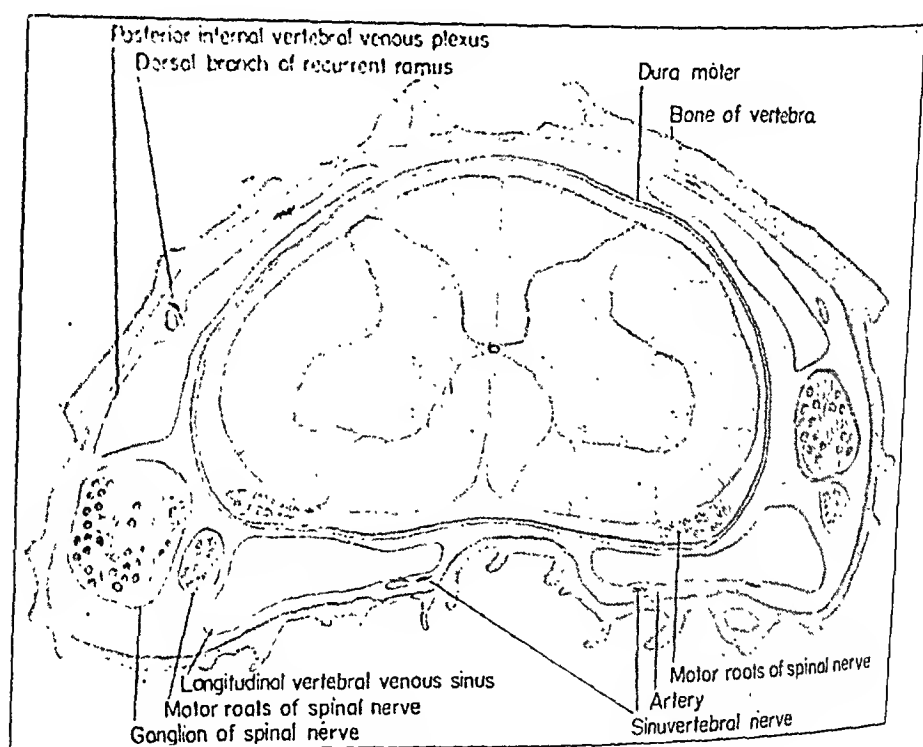


Fig. 2.—Cross section of vertebra.

to the fibers of the spinal nerve roots. In the upper segments studied, on the operative side no intact fibers could be observed in the dorsal region of the spinal canal between the periosteum and the posterior internal vertebral venous plexus.

In all sections of the tissue taken from the intervertebral canals of the animals in which the inferior cervical and the first, second and third thoracic ganglions and the intervening portions of the sympathetic trunk had been removed and the upper thoracic spinal nerve roots divided, bundles of intact unmyelinated fibers were observed lying parallel to the spinal nerves. In some cases, these bundles appeared to be inclosed in the fibrous sheath of the spinal nerve. They usually

included a few myelinated fibers. In the segments in which the spinal nerve fibers had undergone degeneration owing to section of the nerve roots within the vertebral canal, some of the myelinated fibers in the bundles in question, like the unmyelinated ones, had not been affected. The former probably were axons of the spinal ganglion cells located distal to the level at which the nerve roots were divided. The latter undoubtedly were sympathetic fibers which deviated from the sinu-vertebral nerve and entered the intervertebral foramina to join the efferent roots of the spinal nerves. A pathway was thus demonstrated through which sympathetic fibers arising at lower levels might join the upper thoracic and lower cervical nerves and take part in the sympathetic innervation of the upper extremity.

CONCLUSIONS AND SUMMARY

The data obtained in the present investigation support the assumption that most of the constituent fibers of the recurrent branches of the communicating rami, but not all of them, terminate in relation to the blood vessels and the membranes within the vertebral canal. Some penetrate the bone of the vertebrae; some apparently join ventral spinal nerve roots at higher levels than the foramina through which they enter the vertebral canal. The unmyelinated fibers which extend outward in the intervertebral foramina along the ventral spinal nerve roots are undoubtedly components of recurrent rami which enter the vertebral canal at lower levels. The presence of such fibers in preparations of the material taken from the lower cervical and upper thoracic intervertebral foramina in animals from which the sympathetic trunk had been removed on the same side from the lower cervical to the seventh thoracic segment, inclusive, indicates that some sympathetic fibers ascend in the vertebral canal through six or more segments, at least in the upper thoracic region.

The unmyelinated fibers in the nerves in the dorsal region of the vertebral canal, like most of those in the nerves in the ventral region, are obviously derived from the sympathetic trunk ganglia located at the corresponding levels, since they have undergone degeneration in the material taken from the animals which had been subjected to extirpation of the ganglia of the sympathetic trunks in the same segments. These fibers undoubtedly innervate blood vessels in the vertebral canal, including those in the sheaths of the spinal nerve roots in the intervertebral foramina.

The presence in the vertebral canal of sympathetic fibers which arise at lower levels and emerge in the intervertebral foramina in the upper thoracic and lower cervical segments may be correlated with White's

finding, reported by Smithwick (1936),⁶ that complete sympathetic denervation of the upper extremity in the monkey, by section of the anterior roots of the thoracic nerves, requires section of all the roots down as far as the twelfth thoracic segment. It also affords an explanation of the failure in some cases to bring about complete sympathetic denervation of the upper extremity by extirpation of the inferior cervical and upper two or three thoracic segments of the sympathetic trunk. Kirgis (1941)⁷ demonstrated with human cadavers that in a large percentage of cases the third thoracic nerve gives rise to a slender ramus which joins the second thoracic nerve near the junction of the latter with its communicating ramus. This ramus, which includes a large number of unmyelinated fibers, and the intrathoracic ramus of the second thoracic nerve which joins the first (which, as demonstrated by Kuntz [1927],⁸ also includes many unmyelinated fibers) afford a pathway through which sympathetic fibers arising in the third or lower thoracic ganglions of the sympathetic trunk may enter the upper extremity. In the absence of intact rami of this kind, sympathetic fibers which remain intact in the upper extremity after the usual operation for sympathetic denervation probably are fibers which arise at lower levels, ascend in the vertebral canal and join the nerves of the upper extremity through the intervertebral foramina in the upper thoracic and lower cervical segments. In certain cases, complete sympathetic denervation of the upper extremity probably cannot be accomplished without interruption of these fibers.

6. Smithwick, R. H.: Modified Dorsal Sympathectomy for Vascular Spasm (Raynaud's Disease) of the Upper Extremity, *Ann. Surg.* **104**:339, 1936.

7. Kirgis, H. D.: A Ramus Connecting the Third and Second Thoracic Nerves: A Probable Pathway Through Which Sympathetic Fibers from the Third Thoracic Segment May Enter the Brachial Plexus, *Anat. Rec.* **79** (supp. 2):37-38, 1941.

8. Kuntz, A.: Distribution of the Sympathetic Rami to the Brachial Plexus: Its Relation to Sympathectomy Affecting the Upper Extremity, *Arch. Surg.* **15**: 871-877 Dec.) 1927.

TRICHOMONAS INFECTION OF THE MALE GENITOURINARY TRACT

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Trichomonas infection of the male genitourinary tract may not always be the harmless disease it has generally been considered. Standard textbooks have not contained adequate descriptions of this disease in men because relatively few cases have been reported. The literature has contained some excellent contributions on the subject, but as yet much of the work has been controversial.

The diagnosis and treatment of a disease are always of prime importance. In this article the clinical and laboratory diagnoses are given in detail. A new method of treatment for Trichomonas infection in men is presented, which may prove of value for certain aspects of the infection in women.

INCIDENCE

Trichomonas vaginalis was first described by Donné in 1836, but the potential pathologic manifestations were not appreciated until nearly the turn of the century. The first case involving the genitourinary tract of a man was described by Minura in 1894. Up to 1938 Thompson found 104 recorded cases and added 1 case of his own. In 1935 Karnaky reported 38 cases and Anthony 1 case. We do not understand just how many additional new cases Riba and Harrison were reporting in their last paper. We add 1 case of our own, making a total of 145 cases to date, exclusive of Riba and Harrison's report.

Women are admitted to have Trichomonas infection of the genitourinary tract much more frequently than men. For example, Stuhler stated that from 40 to 60 per cent of adult women have *T. vaginalis* infection of the genitourinary tract.

Nitschke gave excellent anatomic, physiologic, biologic and pathologic reasons for the difference of incidence in the two sexes. However, we are not convinced that Trichomonas infection of the genitourinary tract commonly occurs by contamination with Trichomonas hominis from the anus.

On the incidence in men there have been two widely contrasting types of reports. Stuhler found that in 32,000 examinations of prostatic

secretion *T. vaginalis* was found in only 16 or once in every 2,000 examinations. Riba examined 3,000 specimens of prostatic secretion and obtained only 2 that were positive for the organism.

Other investigators have found unusually high rates of incidence. Nitschke demonstrated the presence of the parasite in 5 of 40 cases of so-called nonspecific urethritis. He believed that *T. vaginalis* was present in a fair percentage of the discharges of patients with so-called nonspecific urethritis.

Other authors examined the husbands of women with *T. vaginalis* infection and found that a relatively high number of them were likewise infected. Drummond found that 4 out of 5 such husbands examined were infected with *T. vaginalis*. Karnaky demonstrated that 38 of 150 men examined were infected with this organism.

ETIOLOGIC FACTORS AND PATHOGENESIS

The explanation of *Trichomonas* infection in men is unknown. Leaving aside the personal opinions of authors, we find two types of statistics. One set of figures tends to prove that sexual relations of men with infected women are the most probable source of the disease. For example, Drummond demonstrated *T. vaginalis* infection in 80 per cent of the husbands of infected women, and Karnaky, in 25 per cent.

On the other hand, it must be remembered that according to Stuhler the incidence of *T. vaginalis* infection in all adult women is 40 to 60 per cent, and in those with leukorrhea, 75 per cent. Despite this impressive rate of incidence in women, Stuhler found *T. vaginalis* infection in only 0.05 per cent, and Riba, in 0.06 per cent of the men examined.

A damaged or chronically inflamed urethra with lowered resistance seems to favor *Trichomonas* adaptation and local morbidity and to provide a source for dissemination of the parasites. Out of 23 patients whose records were in Riba and Harrison's office files, 65 per cent admitted previous gonococcic infection; for another 10 per cent there was no information, and 25 per cent gave a history of previous urethral stricture.

The sites of infection in men may be single or multiple. In a series of 23 cases *T. vaginalis* was found in the fresh urethral discharge in 11, in the prostatic secretion in 17 and in the fresh urinary sediment in 16. Karnaky took specimens from under the prepuce. Madsen found a case of *T. vaginalis* infection of the renal pelvis and stated that only 1 other case had been reported.

PATHOLOGY

No good descriptions of the gross lesions of the mucosa in men are available.

As early as 1929 Riba and Perry noted the occurrence of prostatovesiculitis. Heckel observed on rectal examination that the prostate may

be normal in size, shape and consistency or that there may be areas of hardness or infiltration.

Of Riba and Harrison's 23 patients, 61 per cent had urethral stricture; 25 per cent of these gave a history of previously discovered and treated urethral stricture. Of all the cases of urethral stricture of which they had record in their files, *Trichomonas* was identified in 10 per cent. It is evident that *T. vaginalis* was the cause of some of the strictures or tended to settle in urethras which had preexisting strictures.

SYMPTOMS AND SIGNS

Most reports show that men who have this disease present symptoms and signs. One sign observed by most authors is a discharge. It was present in 80 per cent of Riba and Harrison's series and was a mucoïd or purulent urethral discharge. Melvin as well as Nitschke found that the patients complained of a watery discharge from the urethra. Heckel recorded that the disease sometimes started as acute urethritis in which the discharge had a frothy, bubbly appearance.

Heckel stated that the symptoms of *Trichomonas* infection of the prostate are the same as those of nonspecific urethritis, persistent urethral discharge and morning drop associated with various other genitourinary complaints. His description of the prostate from rectal examination has already been given. He stated that it is never tender or swollen as in acute gonorrheal prostatitis.

Manwell noted the relationship of urinary symptoms to *Trichomonas* infection, even though other authors have failed to observe this.

In some of Karnaky's cases there was itching of the glans penis.

LABORATORY DIAGNOSIS

The disease is not common. However, there are probably more cases than are diagnosed.

To find more of these cases and attempt to clarify a good many points about this disease in men, we suggest that appropriate specimens be taken as regularly as feasible in general examinations. Appropriate specimens should be obtained from all men with nonspecific urethritis. Husbands of women with *T. vaginalis* infections should be carefully investigated.

Methods of Collecting Specimens.—Specimens should be obtained from the prepuce, the urethra, the urine and the prostate. It must be remembered that the fragility of *T. vaginalis* precludes successful detection unless care is exercised in handling.

If there is sufficient material, the prostatic fluid is allowed to drip directly into an open sterile Petri dish, 7.5 cm. in diameter. The dish is then covered.

If there is only a scanty amount of fluid, separate sterile cotton-tipped applicator sticks are used to collect material from the prepuce, the urethra and the prostate.

The swab is small, not over 3 mm. in diameter. It is tightly wound so that the flagellates will have difficulty in penetrating between the cotton fibers. If they do penetrate and become enmeshed in the fibers below the surface, they are probably lost for purposes of identification because, through adherence, among other factors, they will be trapped, and the examiner will be unable to express them onto the slide.

Immediately after the specimen is taken, the cotton-tipped end of the swab is placed in a separate small sterile test tube containing 0.5 cc. of 0.85 per cent sodium chloride solution. Each tube has a sterile nonabsorbent cotton stopper, which is put back in place as soon as the applicator stick is inserted.

Urine is collected in a sterile container.

Dry smears are made of prostatic and urethral material in the usual manner. These are appropriately stained and examined, particularly for gonococcus, *Streptococcus subacidus* and *Monilia albicans*.

Methods of Examination.—It is our experience that accurate reports on *Trichomonas* can be made only by the advanced laboratory worker.

(a) Direct Examination of Specimens Obtained in Small Petri Dishes: A sufficient amount of the fluid is removed from the Petri dish with a sterile Pasteur pipet having a long tip of capillary diameter. The fluid (0.01 cc.) is placed on a sterile glass slide kept at a temperature approximating 90 F. It is covered with a sterile no. 1 cover slip. Microscopic search is instituted with a magnification of approximately 640 (10x oculars and high dry objective). If no movement is noted, additional preparations are examined, fifteen minutes each, before being pronounced negative. If kept at 98.6 F., trichomonads are viable in prostatic secretions for an average period of six hours.

(b) Examination Following Centrifugation of Wet Specimens: In our opinion this has not been a common enough practice. Tests should not be pronounced negative until this method has been employed.

For specimens obtained in sodium chloride solution, the procedure is as follows: If a prolific discharge has not been obtained, the swab is thoroughly rinsed in the solution, being pressed and rotated against the wall of the test tube to express as much liquid as possible, before it is discarded. The sterile conic test tube is centrifuged for five minutes at 3,000 revolutions per minute. The supernatant fluid is removed, and the sediment in the bottom of the tube is placed on a sterile glass slide under conditions similar to those described for direct examination. Trichomonads adhere to the fibers of the swab, and this makes it necessary to handle it as described. Omission of centrifuging would leave the parasites in far too dispersed a condition to be studied conveniently. The importance of these maneuvers is seen in the fact that Magath, who merely shook these swabs, obtained positive evidence of *T. vaginalis* infection in only 20.8 per cent of his series of 250 women.

In cases in which the discharge has been fairly prolific, the swab is pressed firmly against a slide and rotated with continuous maintenance of pressure at an angle of approximately 30 degrees from horizontal. Magath, who merely shook these swabs onto the slides, reported that 1.92 per cent of his cultures were failures.

Urinary specimens are centrifuged and mounted in the same way as specimens of nonprolific discharge in solution of sodium chloride.

(c) Methods of Examination Not Ordinarily Utilized: Certain maneuvers are of value to the research worker and advanced technician. For instance, determination may be made of the number of trichomonads present in a measured volume of solution.

Differential Characteristics of Species of Trichomonas

Species	Variation in			Structure			Incidence in Temperature Zone, per Cent	Culture		
	Length, Microns	No. of Anterior Flagella	Average Length, Microns	Parabasal * Apparatus	Size of Chromatic Basal Rod and Axoneme	Cytoplasm		Optimal Mediums †	Gas Production	Odor
T. vaginalis....	7 to 23	4	13	Sausage-shaped	Less than one-half the body length	Granules seen; vacuoles rare; light-staining	50 to 60 (women)	L. E. S. or placenta agar	Very marked with pressure	Foul and slightly pungent
Trichomonas hominis	7 to 14	3 to 4	8	Oval	Nine-tenths to entire body length	No granules seen; vacuolated; deep-staining	1.7	L. E. A. or blood agar	Small	Unpleasant
Pentatrichomonas ardin deffell	6 to 16	5	9							
T. buccalis.....	6 to 12	4	7.5	Disc-shaped	Three-fourths body length	Few granules with no definite arrangement; vacuolated; deep-staining	13 to 24	L. E. S. or placenta agar	Moderate	Foul, like bad breath

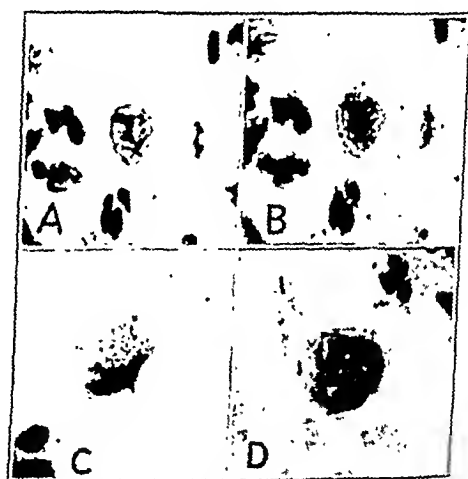
* Visualized only with stains containing osmic or chromic acid.

† L. E. S. indicates Boeck and Drobobay's Locke solution-egg-serum medium, in which equal parts of Locke solution and human blood serum are added to egg slants prepared with Locke solution. L. E. A. indicates Drobobay's modification of the aforementioned medium, in which a 1 per cent solution of crystallized egg albumin in Locke solution is substituted for the mixture of Locke solution and human blood serum. The formulas for these mediums are contained in Craig, C. F., and Faust, E. C.: Clinical Parasitology, ed. 2, Philadelphia, Lea & Febiger, 1940, p. 660.

There are also cultural methods which are most useful for making blood examinations, for increasing the total number of trichomonads prior to staining for species identification and for differentiation of the species. The traps of Stone and Reynolds give bacteria-free cultures of *T. hominis* and are apparently applicable in pure culture studies of the three common species of *Trichomonas*. The cultural characteristics of the different species are given in more detail in the table.

There are two methods which we do not recommend. Moist preparations stained with 0.1 per cent safranin are used mainly for the differentiation of *T. vaginalis* from pus cells, but since safranin is a negative stain, its accuracy is dubious. The hanging drop procedure is valuable but time consuming and, in our opinion, unnecessary. Trichomonads are not crushed by the pressure of a cover slip.

Identification of T. Vaginalis (photomicrograph).—Identification of *T. vaginalis* is made on the basis of the motility, the manner of progress, the gross appearance and the size of the flagellate. The parasite is motile. The anterior flagella have a peculiar whiplike motion, which in an active trichomonad occurs with a simul-



Photomicrographs of *Trichomonas vaginalis*; hematoxylin stain; $\times 1900$.

A, usual body form of the young flagellate. B, an artificial light cone sometimes confused with the cyst form. Note the two visible flagella. C, surface focus, showing chromatic basal rod extending across cytoplasm and starting from anterior blepharoplast. D, form often seen in heavy infections; the two flagella are again visible. Note the granules in the cytoplasm.

taneous forward propulsion and counterclockwise rotation. If the flagellate is hindered by pus and epithelial cells or its motion is reduced, one may see that one flagellum whips forward and backward over the body surface, while the others appear to move forward only as far as the anterior plane and then back. This differential motion of the flagella helps to distinguish the trichomonads from other protozoa which may be present. The organism without the flagella is 8 to 16 microns in width and 15 to 26 microns in length.

It may be of vital interest to differentiate *T. vaginalis* from the other species of *Trichomonas*. The table may prove of assistance.

TREATMENT

The treatment of this infection in men has been multifarious and disputed and consequently somewhat confusing. In general, the forms of

therapy have been those generally used by the specialist in genitourinary diseases of men.

Much more definite advances have been made in the treatment of *T. vaginalis* infections in women because of the larger number of cases. Two compounds, acetarsones and silver picrate, have been used with considerable success. The literature is replete with articles attesting their therapeutic efficacy. In treating a man, it seems logical to use one of the aforementioned antiseptics which have already proved their parasitocidal action on *T. vaginalis* in numerous cases of infection in women.

An acetarsones preparation is incorporated into a 2 inch (5 cm.) size 14 (French) urethral suppository. The patient is instructed to insert this after allowing warm water to run on it for a short time so that it will mold more easily to the contour of the urethra. One is inserted after urination in the morning and evening. To obtain prostatic smears, the prostate is massaged lightly about every third day for ten days and every two weeks for about two months.

Although it has not been proved that a woman can reinfect a man, it seems best to have the patient use some precautions. It is not wise for him to have sexual intercourse during the period that specimens obtained from him show *T. vaginalis*. For a few weeks after such a period it is probably best that he use condom protection. It would be interesting to cure the man but not the woman and then observe the effects of intercourse on the man. However, from a nonexperimental standpoint it is more acceptable to treat the disease in the woman coincidentally with that in the man.

The rapid cure of urinary symptoms in the case to be reported gave rise to an idea which it is proposed to use in the treatment of women with *T. vaginalis* infection and urinary symptoms. The clearing up of urinary symptoms is often delayed in these patients, even though the *Trichomonas* infection of the vagina is receiving adequate therapy. Of course, proper treatment will be administered for the *Trichomonas* infection of the vagina, but in addition urethral suppositories incorporating an acetarsones preparation will be used twice daily in these women to see whether a quick cure of the annoying urinary symptoms cannot be obtained.

REPORT OF A CASE

G. M., a 25 year old white man, a university student, was first seen Sept. 5, 1940. He had had sexual intercourse with one woman on repeated occasions in the preceding three months. Two weeks prior to his first reporting to us, he had had intercourse without protection on the last night of the woman's menstrual period.

Five days later he had a burning, irritated feeling just inside the external urethral meatus. After six more days he had a feeling of general debilitation, a dull ache in his penis and an increased tendency to urinate accompanied by tenesmus and burning. He denied that he had used therapy of any kind, that there

had been any discharge from the penis or that there had been previous venereal or genitourinary infections.

Physical examination revealed no urethral discharge. The prostate showed 2 plus enlargement (on a basis of 1 to 4) and irregular areas of 2 plus hard infiltration. The urethra and prepuce were normal. A direct prostatic specimen showed four to five trichomonads identified as *T. vaginalis* per high dry field. The dry smear had no intracellular or extracellular gram-negative diplococci, *Streptococcus subacidus*, *Monilia albicans* or pus cells.

Twelve urethral suppositories incorporating an acetarsone preparation were prescribed; this was the total extent of the medication. He was told to use one before retiring and in the morning after urination. The prostate was massaged on September 7 and 10, there being only one-third as much enlargement and one-half as much hard infiltration on September 10 as on September 5. Specimens of prostatic fluid taken on September 13, 16 and 22 and October 8 and 18 were uniformly negative for *T. vaginalis*. The patient was free of symptoms by September 10.

The woman was found to have *T. vaginalis* infection and quickly responded to therapy.

The patient had protected intercourse with the same woman on September 16. He continued in this manner about twice a week until October 17, after which he had unprotected intercourse without reinfection of himself or the woman.

COMMENT

While certain of the laboratory methods which we have described may have been utilized by other workers, search of the literature to date fails to reveal publication of the following facts:

1. It is advantageous to allow the prostatic fluid to drip directly into the Petri dish; this minimizes manipulation and contamination.

2. The relatively sterile technic used to eliminate contaminating bacteria and fungi makes it possible to report the identification of protozoa, easy technic that we have been able to find.

3. The improved type of swab which we have described helps to minimize the percentage of falsely negative reports.

4. The careful expression of the liquid material from the swabs, a hitherto unpublished method, has advantages, which we have carefully enumerated.

5. The routine centrifuging of wet specimens which is strongly urged, coupled with the careful, time-consuming laboratory examination, gives the worker a more reasonable sense of satisfaction when he reports a specimen as negative for *Trichomonas*.

6. The careful use of the description of *T. vaginalis* and the easily available information in the differential diagnostic table (which, by the way, is the first of its kind published) certainly minimizes the percentage of errors. However, if a person is unable to recognize the organism for which he is looking, all the refinements mentioned would obviously be

futile. No claims are made that every one can identify this flagellate. In the table special attention must be paid to the chromatic basal rod and axoneme, under "Structure." The axoneme, of course, includes the attached portion of the posterior flagellum. Therefore, the point of emergence of the posterior flagellum is of great diagnostic importance.

A new method of treatment for *Trichomonas* infection in men has been presented. Attention has been called to the fact that this mode of therapy may be of value in curing the urinary symptoms sometimes encountered in *T. vaginalis* infections of women. Since 40 to 60 per cent of women have this infection, it appears that this proposed therapeutic method is worth cognizance and experimental trial.

SUMMARY

The diagnosis, particularly from a laboratory aspect, of *Trichomonas vaginalis* infections of the male genitourinary tract is presented in some detail.

A new form of treatment for *Trichomonas* infection in men is given. This method may prove of value in certain aspects of the disease sometimes encountered in women.

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BIBLIOGRAPHY

- Allen, E. D.: *Trichomonas Vaginalis* Vaginitis, *Am. J. Surg.* **33**:523 (Sept.) 1936.
- Jensen, L. B., and Wood, I. H.: Clinical and Bacteriologic Observations in *Trichomonas Vaginitis*, *Am. J. Obst. & Gynec.* **30**:565 (Oct.) 1935.
- Ayer, E. W., and Neil, J. M.: Protozoa in the Urinary Tract, *J. A. M. A.* **94**: 1489 (May 10) 1930.
- Balkow: Zur Bedeutung der *Trichomonas vaginalis* als Erreger einer Kolpitis purulenta und der unspezifischen Urethritis beim Manne, München. med. Wchnschr. **82**:331 (Feb. 28) 1935.
- Bishop, A.: Systematic Position of "*Trichomonas Keilini*," *Parasitology* **31**:469 (Dec.) 1939.
- Bland, P. B.; Wenrich, D. H., and Goldstein, L.: *Trichomonas Vaginitis* in Pregnancy, *Surg., Gynec. & Obst.* **53**:759 (Dec.) 1931.
- and Rakoff, A. E.: The Incidence of *Trichomonads* in the Vagina, Mouth and Rectum, *J. A. M. A.* **108**:2013 (June 12) 1937.
- Capek, A.: Die Flagellaten-Urethritis des Mannes: Vorläufige Mitteilung, *Med. Klin.* **23**:1535 (Oct. 7) 1927.
- Cornell, E. L., and Riba, L. W.: Treatment of *Trichomonas Vaginalis* and *Trichomonas* in Male, *Surg., Gynec. & Obst.* **63**:511 (Oct.) 1936.
- Craig, C. F., and Faust, E. C.: *Clinical Parasitology*, ed. 2, Philadelphia, Lea & Febiger, 1940.
- Cutter, R. K.: The Use of Large Volume Intravenous Injections, *J. A. M. A.* **106**:1250 (April 11) 1936.
- Dastidar, S. K. G.: *Trichomonas* Infection in Urine, *Indian M. Gaz.* **60**:160 (April) 1925.

- Davis, C. H., and Colwell, C.: *Trichomonas Vaginalis*, J. A. M. A. **92**:306 (Jan. 26) 1929.
- Dobell, C.: The Common Flagellate of the Human Mouth, *Trichomonas Tenax* (O. F. M.): Its Discovery and Its Nomenclature, *Parasitology* **31**:138 (April) 1939.
- Dock, G.: Flagellate Protozoa in the Freshly Passed Urine of a Man, *M. News, Philadelphia* **65**:690, 1894.
- Trichomonas* as a Parasite of Man, *Am. J. M. Sc.* **111**:1, 1896.
- Donné, L.: Animalcules observés dans les matières purulentes et le produit des sécrétions des organes génitaux de l'homme et de la femme, *Compt. rend. Acad. d. sc.* **3**:385, 1836.
- Drummond, A. C.: *Trichomonas* Infestation of the Prostate Gland, *Am. J. Surg.* **31**:98 (Jan.) 1936.
- Greenhill, J. P.: The Treatment of *Trichomonas Vaginalis* Vaginitis, J. A. M. A. **96**:1862 (May 30) 1931.
- Grimm, O.: Die *Trichomonas vaginalis* Urethritis beim Manne, *Dermat. Ztschr.* **59**:314 (Oct.) 1930.
- Heckel, N. J.: Trichomoniasis of the Genito-Urinary System, *M. Clin. North America* **21**:319 (Jan.) 1937.
- Hees, E.: Epidemic Trichomonad Infections and Experimental Studies Thereon, *J. Egyptian M. A.* **21**:813 (Dec.) 1938.
- Hegner, R. W.: Effect of Changes of Diet on Incidence, Distribution and Number of Certain Intestinal Protozoa and Toad Tadpoles, *J. Parasitol.* **9**:51 (Dec.) 1922.
- Trichomonas Vaginalis* Donné, *Am. J. Hyg.* **5**:302 (May) 1925.
- Ingestion of Red Blood Corpuscles by Trichomonad Flagellates, J. A. M. A. **90**:741 (March 10) 1928.
- Hibbert, G. F.: Significance of Streptococcus in (So-Called) *Trichomonas Vaginalis* Vaginitis, *Am. J. Obst. & Gynec.* **25**:456 (April) 1933.
- Jenkins, P. K.: Urethritis Due to *Trichomonas*, *New England J. Med.* **208**:687 (March 30) 1933.
- Johnson, W. T.: Personal communication to the author.
- Karnaky, K. J.: Karnaky's Trichomonal and Leukorrhea Research, *Bull. Jefferson Davis & John Sealy Hosps.*, 1935, no. 8.
- Katsunuma, S.: Présence de trichomonas vaginalis dans l'urine d'un jeune garçon, *Bull. Soc. path. exot.* **17**:216, 1924.
- Kölliker, A., and von Scanzoni, F. W.: Das Sekret der Schleimhaut der Vagina des Cervix Uteri, *Beitr. z. Geburtsh. u. Gynäk.* **2**:128, 1855.
- Kofoed, C. A., and Swezy, O.: On the Morphology and Behavior of Pentatrachomonas Ardin Delteili (Derrieu and Raynaud), *Univ. California Publ. Zool.* **20**:373, 1923.
- Hinshaw, H. C., and Johnstone, H. G.: Animal Parasites of the Mouth and Their Relation to Dental Disease, *J. Am. Dent. A.* **16**:1436 (Aug.) 1929.
- Kunstler, J.: Analyses microscopiques des urines d'un malade atteint de pyélite consécutive à une opération de taille, *J. de méd. de Bordeaux* **13**:249, 1833-1884.
- Lewis, B., and Carroll, G.: A Case of *Trichomonas Vaginalis*: Infection of the Kidney Pelvis, *J. Urol.* **19**:337 (March) 1928.
- McGree, C. F., and McNeil, E.: Experimental Inoculations of Trichomonads from Man into Prostate Gland of Rats, *Proc. Soc. Exper. Biol. & Med.* **36**:587 (June) 1937.

- Madsen, A. C.: A Case of Trichomonas Infection of Kidney Pelvis, West Virginia M. J. **29**:356 (Aug.) 1933.
- Magath, T. B.: The Diagnosis of Trichomonas Vaginalis, Am. J. Obst. & Gynec. **35**:694 (April) 1938.
- Manwell, E. J.: Urinary Symptoms in Relation to Trichomonas Vaginalis Infestation, New England J. Med. **211**:567 (Sept.) 1934.
- Marchand, F.: Ueber das Vorkommen von Trichomonas im Harne eines Mannes, nebst Bemerkungen ueber Trichomonas vaginalis, Centralbl. f. Bakt. **15**:709, 1894.
- May, F.: Trichomonas vaginalis Infektion der Harnwege, Ztschr. f. urol. Chir. **35**:213, 1932.
- Melvin, P. D.: Urinary Infections with Trichomonas Vaginalis in the Male, J. Florida M. A. **24**:391 (Jan.) 1938.
- Miller, J. R.: Contrast Stain for Rapid Identification of Trichomonas Vaginalis, J. A. M. A. **106**:616 (Feb. 22) 1936.
- Minura, K.: Trichomonas vaginalis in frischgelassenen Urin eines Mannes, Centralbl. f. Bakt. **16**:67, 1894.
- Nitschke, P. H.: Trichomonas Vaginalis Infestation in the Male, J. A. M. A. **107**:12 (July 4) 1936.
- Comments on Trichomonas Vaginalis Infestation in the Male, Urol. & Cutan. Rev. **41**:190 (March) 1937.
- Ockuly, E. A.: Trichomonas Vaginalis Infestation of Male Genito-Urinary Tract, Ohio State M. J. **32**:1086 (Nov.) 1936.
- Paulson, M.: An Accurate Method for the Numerical Determination of Endamoeba Histolytica in Vitro, and Its Possible Use with Other Intestinal Protozoa: Suggested Clinical Application, Am. J. Trop. Med. **12**:387 (Sept.) 1932.
- The Numerical Determination of Trichomonas Hominis in Urine and Its Practical Implications in Genitourinary Parasitism, J. Lab. & Clin. Med. **22**:646 (March) 1937.
- Pelouze, P. S.: Trichomonas Infestation of the Prostate, Urological Correspondence Club, March 5, 1934.
- Pittman, J. H.: Urological Correspondence Club and personal communication to the author, Oct. 11, 1937.
- Riba, L. W.: Trichomonas Urethritis, J. A. M. A. **96**:2100 (June 20) 1931.
- and Perry, E.: Trichomonas Prostate Vesiculitis, J. Urol. **22**:563 (Nov.) 1929.
- and Harrison, R. M.: Strictures of the Male Urethra and Trichomonas Vaginalis, Surg., Gynec. & Obst. **71**:369 (Sept.) 1940.
- Rosenthal, D. B.: Urinary Infection with Trichomonas Vaginalis in the Male, M. J. Australia **1**:782 (June 27) 1931.
- Sayer, J. H.: Vulvovaginitis Pruritic Trichomonalis, Northwest Med. **30**:278 (June) 1931.
- Smith, J. F.: Trichomonas Vaginalis in Prostate, Urol. & Cutan. Rev. **37**:615 (Sept.) 1933.
- Stein, I. F., and Cope, E. J.: Trichomonas Vaginalis (Donné), Am. J. Obst. & Gynec. **25**:819 (June) 1933.
- Stone, W. S., and Reynolds, F. H. K.: Practical Method of Obtaining Bacteria Free Culture of T. Hominis, Science **90**:91 (July 26) 1939.
- Stuhler, L. G.: Trichomonas Vaginalis Infestation in Prostate Gland, Proc. Staff Meet., Mayo Clin. **8**:221 (April 12) 1933.

- Swift, B. H.: *Trichomonas Vaginalis* Vaginitis as Cause of Pruritus Vulvae, *M. J. Australia* **1**:123 (Jan. 23) 1937.
- Thompson, R. F.: *Trichomonas Vaginalis* Infestation in the Male, *Southwest Med.* **22**:133 (April) 1938.
- Visler, J. W.: Vesical Infection with *Trichomonas Vaginalis*, *J. A. M. A.* **92**:2098 (June 22) 1929.
- Wahlén, O. S.: Urethritis in Man Caused by *Trichomonas Vaginalis*, *Svenska läk.-tidning.* **31**:137 (Feb. 9) 1934.
- Wright, F. R.: *Trichomonas Vaginalis* in the Male Urethra, *Urol. & Cutan. Rev.* **37**:335 (May) 1933.
- Zahorsky, J.: Infection by the *Trichomonas Hominis*, *M. Clin. North America* **11**:315 (Sept.) 1927.

MEDIASTINAL EMPHYSEMA AND BILATERAL PNEUMOTHORAX FOLLOWING RADICAL DISSECTION OF THE NECK

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Surgical procedures about the neck which allow ample opportunity for partial blocking of the upper respiratory passages and for opening the mediastinum provide a situation most favorable for the development of mediastinal emphysema. Berry¹ reported 4 cases of thyroidectomy and 1 of tracheotomy in which mediastinal emphysema and bilateral pneumothorax were present at death, which occurred either on the operating table or shortly afterward. At autopsy, in every case, the pleura was intact, and there was no interstitial emphysema present; air, then, must have entered through the operative site. Keis² reported 8 cases of thyroidectomy, in 5 of which mediastinal emphysema was observed at autopsy. In 4, bilateral pneumothorax was present. In all of these cases, the tracheal and bronchial passageways were normal, and the lungs showed no interstitial emphysema.

Keis expressed the opinion that mediastinal emphysema occurring during operations on the upper portion of the neck is less frequent in young people because the thymus and healthy mediastinal connective tissue protect the patient from the development of this complication. In the older group, previous infection in or around the mediastinum with the formation of adhesions may serve to block the entrance of air at the time of operation.

REPORT OF A CASE

G. C., a 58 year old man, was first admitted to the Ellis Fischel State Cancer Hospital on Sept. 11, 1940. In 1936 a cancer of the lip had been treated elsewhere with a white powder. In August 1940, the lip became somewhat swollen, slight ulceration occurred at the site of the previous lesion of the lip, and small lumps were noted in the neck. The past history was noncontributory.

From the Ellis Fischel State Cancer Hospital, Columbia, Mo.

1. Berry, H. J.: Interstitial Emphysema and Pneumothorax After Operations, *Lancet* 1:996, 1940.

2. Keis, J.: Studien zur Genese des Mediastinalemphysems und des Pneumothorax bei Kropfoperationen, *München. med. Wchnschr.* 81: 669, 1934.

Physical Examination.—The patient was a well developed and well nourished man. The teeth were extremely carious. An ulcerating, fungating mass measuring 5 by 5 by 2 cm. replaced most of the lower lip and extended down to the chin. The lesion involved the right oral commissure. Enlarged lymph nodes were palpable in the submental and right submaxillary triangles and in the deep cervical region. The largest node was located in the submaxillary triangle and measured approximately 2 cm. in diameter. The lungs were clear and the heart normal. The blood pressure was 120 systolic and 85 diastolic.

Laboratory Examination.—The urine showed a slight trace of albumin. The blood was normal. Three biopsies of the lesion of the lip showed hyperkeratosis and chronic inflammation.

Clinical Course.—The patient was given an intensive course of roentgen therapy to the lip and to the lymph nodes of the upper cervical region. This treatment resulted in marked regression of the lesion and some decrease in the size of the metastatic nodes. He was discharged from the hospital on November 10.

Second Admission.—The patient was readmitted on December 6. The lip showed a rather large defect, the edges of which were entirely healed, soft and pliable. There was no clinical evidence of residual carcinoma in the area of the primary lesion. The previously described mass in the submaxillary triangle had increased to 2.5 cm. in diameter but was not attached to the mandible. Posterior to this and beneath the tail of the parotid gland was another mass which measured 1 cm. in diameter. In the submental triangle and the deep cervical chain, involvement of the lymph nodes was not apparent. Complete dissection of the right side of the neck and the submental triangle was thought advisable.

Surgical Procedure.—On December 12, with the patient under anesthesia induced by administration of avertin with amylene hydrate followed by insufflation of ether, a complete dissection of the right side of the neck was started. After elevation of the flaps, the sternocleidomastoid muscle was sectioned from its inferior attachment, and the internal jugular vein was isolated, doubly ligated and sectioned just above its junction with the subclavian veins. Suddenly, while the work in this area was going forward, a sucking and blowing noise was heard. It was thought that the apical parietal pleura had been opened, and the area of questionable defect was carefully closed with interrupted silk sutures, after which the sound stopped.

As the operation progressed, an occasional slight sucking noise was heard, but repeated investigation failed to reveal its cause. The operation otherwise proceeded uneventfully, except for some difficulty in maintaining a perfectly free airway.

Throughout this three hour procedure, the blood pressure and pulse remained at a constant normal level. The patient showed no signs of anoxemia or cyanosis until the operation was nearly terminated, when sudden and extreme cyanosis developed. Oxygen was administered through a tracheal catheter, and artificial respiration was given. In spite of these measures the patient's condition grew steadily worse, and he died in cardiorespiratory failure.

After death, a needle was inserted into the right pleural cavity, and 20 cc. of air was removed. A postmortem anteroposterior roentgenogram of the chest was taken, and evidence of mediastinal emphysema and bilateral pneumothorax was seen. Unfortunately, no lateral views of the chest or roentgenograms of the abdominal cavity were taken.

Autopsy.—The anatomic diagnoses were: subcutaneous emphysema, mediastinal emphysema, bilateral pneumothorax, distention of the stomach, hemangiomas of the liver, adenomas of the kidneys, polyposis of the large bowel, benign hypertrophy of the prostate gland and cortical adenoma of an adrenal gland. The microscopic diagnoses confirmed the gross. Section of the surgical specimen showed epidermoid carcinoma present in a large node of the submaxillary triangle. All other nodes were free of evidence of tumor.

The body was fairly well developed. There was pronounced postmortem lividity of the face and dependent portions. There was slight subcutaneous emphysema in the loose tissues of the neck just above the sternum. When the peritoneal cavity was opened, the right diaphragm was strikingly convex. Bilateral pneumothorax was demonstrated by the puncture of both rib cages under water. With the removal of the sternum, numerous blebs were seen in the soft fatty



Bilateral pneumothorax. The arrows indicate the edges of the partially collapsed lungs.

tissue overlying the heart. Emphysema extended throughout the anterior and posterior mediastinum.

The lungs showed no evidence of interstitial emphysema. There were old bilateral adhesions, causing complete obliteration in the upper thirds of both pleural cavities. Rupture of mediastinal blebs with separation of the parietal and visceral pleura had caused formation of bilateral pneumothorax. This bilateral pneumothorax was not complete because tough fibrous adhesions between the parietal and visceral pleura at the apices prevented total collapse of the lungs.

Careful attention was given to the parietal pleura in the right apex, but no evidence of a surgical wound was found.

The heart weighed 300 Gm.; slight dilatation of the right auricle was evident. The stomach was much distended, and on puncture a large amount of air smelling of ether rushed forth. There were small hemangiomas in the liver. Tubular adenomas in the kidneys measured from 5 mm. to 1 cm. in diameter. A marked polyposis of the ascending colon was present.

COMMENT

Macklin,³ experimenting with cats and other animals, demonstrated the pathway by which air can reach the mediastinum from the upper respiratory passages. Under increased pressure air breaks through alveoli, reaches the interstitial tissues, travels along the sheaths of the pulmonary veins and arteries, and finally enters the mediastinum. If air continues to be pumped into the mediastinum, the rupture of emphysematous blebs on the mediastinal pleural surface may cause unilateral or bilateral pneumothorax. Therefore, if this mechanism had been at work in our case, there should have been some interstitial emphysema; careful examination at autopsy showed none. Direct entrance of air through the wall of any thoracic organ into the mediastinum may cause mediastinal emphysema. There was no evidence of any break in the continuity of the mucosa of the bronchi, trachea or esophagus.

Infections such as influenza,⁴ pertussis, diphtheria and other acute diseases of the lung may provide an entry for air into the interstitial tissue. Gross and microscopic examination of the lungs in our case showed no evidence of infection in the trachea, bronchi or alveoli.

Hamman⁵ wrote of spontaneous mediastinal emphysema, but that is always accompanied by a break in the alveolar wall with interstitial emphysema, and, as has been stated, there was none of this in our case.

We believe that the only way air could have entered the mediastinum was through the operative site because no interstitial emphysema was present in the lungs. Air could not have entered the pleural cavities through the surgical incision directly, because the pleura of the left lung was not approached by the dissection and because autopsy revealed the pleura of the right lung to be uninjured. The pleural spaces in both apexes were obliterated by adhesions. The presence during the operation of some obstruction to the airway increased the intrathoracic negative pressure on inspiration and induced air to enter the thorax through the only other opening available. With each inspiration air was sucked into the open anterior mediastinum, where it became trapped in the soft tissues. As the condition progressed, large blebs of air appeared beneath the mediastinal pleurae, and it was the rupture of these that produced pneumothorax.

3. Macklin, C. C.: Transport of Air Along Sheaths of Pulmonary Blood Vessels from Alveoli to Mediastinum, *Arch. Int. Med.* **64**:913 (Nov.) 1939.

4. Torrey, R. G., and Grosh, L. C.: Acute Pulmonary Emphysema Observed During the Epidemic of Influenzal Pneumonia at Camp Hancock, Georgia, *Am. J. M. Sc.* **157**:170, 1919.

5. Hamman, L.: Spontaneous Mediastinal Emphysema, *Bull. Johns Hopkins Hosp.* **64**:1, 1939.

It is conceivable that with the development of mediastinal emphysema there will be increasing obstruction to venous return. The mechanical and physiologic changes are similar to those found in cardiac tamponade. In the case presented, bilateral pneumothorax added further embarrassment to the respiratory mechanism, and with the pulmonary collapse oxygen exchange was interfered with to such an extent that the patient died of heart and respiratory failure.

Artificial respiration was probably contraindicated, for, as Keis² mentioned, this tends to increase mediastinal pressure and facilitate the production of pneumothorax.

The presence of multiple hemangiomas of the liver, tubular adenomas of the kidneys, cortical adenoma of an adrenal gland and marked polyposis of the large bowel causes speculation as to whether or not some congenital anomaly might not have existed in the mediastinum.

PREVENTION AND TREATMENT

During an operation in the lower portion of the neck the possibility of the development of mediastinal emphysema should be kept in mind. Prevention can best be accomplished by making certain that a perfectly free airway is maintained when the limits of the mediastinum are approached.

It is extremely important to recognize the condition in its early stages, since the establishment of an adequate airway will decrease the negative intrathoracic pressure on inspiration and may help prevent abnormal ingress of air into the thorax. If the establishment of an adequate airway does not suffice, the opening into the mediastinum should be closed by packing or closing the soft tissues or by terminating the operation and closing the wound if necessary. In our case the surgeon did not appreciate the situation and was misled to believe the sucking noises were the result of a small leak through the parietal pleura. The signs were insidiously unimpressive until the sudden and complete collapse of the patient.

If mediastinal emphysema is not recognized until after bilateral pneumothorax has occurred, emergency aspiration of both pleural spaces should be done. If aspiration by syringe and needle does not afford adequate decompression, an intercostal catheter may be inserted into the chest and connected to a suction apparatus or to a water-sealed drainage bottle. Artificial respiration is contraindicated.

Mediastinal emphysema is probably much more frequent than is suspected. Failure to think of this complication during an operation on the neck, failure to take roentgen films of the chest and, if the patient dies, failure to check for pneumothorax and to look for mediastinal emphysema may result in an erroneous diagnosis.